Supreme Court, U.S.
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No. _____

IN THE

Supreme Court of the United States

PHARMASTEM THERAPEUTICS, INC.,
Petitioner,

v.

VIACELL, INC.; CRYO-CELL INTERNATIONAL, INC.; CORCELL, INC.; and CBR SYSTEMS, INC. (formerly known as CORD BLOOD REGISTRY, INC.),
Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

In this case, a divided court of appeals declared petitioner's patent claims invalid as obvious in view of certain prior art. It did so even though (a) the Patent and Trademark Office ("PTO") had upheld the validity of the claims over that art in two examinations and three reexaminations, (b) a jury found the claims valid over that art, and (c) the district court confirmed that the evidence was sufficient to support the jury's verdict. In finding obviousness, the majority relied on an earlier hypothesis that a biological premise of the invention might be true—even though the hypothesis was unproven, the patented approach was widely rejected as unviable, and the claimed technique (once proven valid and practical) revolutionized the field and pioneered an industry.

The questions presented are:

1. To what extent courts should defer to PTO determinations that patent claims are valid over particular prior art references when a defendant challenges the validity of the same claims over the same art in an infringement lawsuit. Relatedly, whether the presumption of patent validity of 35 U.S.C. § 282 strengthens when the PTO has considered and rejected a contention that a patent claim is invalid over prior art.

2. Whether a mere hypothesis of a biological fact necessarily renders obvious a medical technique that builds upon that fact—even when the prior hypothesis was unproven, the technique remained unperformed and unenabled, those skilled in the art rejected the claimed approach as unviable, and the invention was greeted with surprise and great acclaim.

PARTIES TO THE PROCEEDINGS AND RULE 29.6 STATEMENT

In addition to the parties named in the caption, the original complaint in this case named Nustem Technologies, Inc., StemCyte, Inc., Birthcells Technology, Inc., and Bio-Cell, Inc. as defendants. None of those parties participated in the appeal. The district court entered a default judgment against NuStem, StemCyte was dismissed from the case following a settlement, and Birthcells and Bio-Cell both went bankrupt before trial.

Petitioner PharmaStem Therapeutics, Inc. has no parent corporation, and no publicly held company owns 10% or more of its stock.

TABLE OF CONTENTS

Table of Authorities v

Opinions Below 1

Jurisdiction 1

Pertinent Statutes 1

Statement of the Case 2

A. The Patented Inventions, Their Advancement Over the Prior Art, and the Industry They Have Spawned 3

B. The PTO's Issuance of the Patents and Its Repeated Confirmation of Their Validity in Later Reexaminations 7

C. The Jury's Findings That the Claims Are Valid, the District Court's Affirmation of That Finding, and the Federal Circuit's Split Decision Reversing and Invalidating the Claims ... 11

Argument for Granting the Writ 17

I. Review Is Warranted So That This Court Can Clarify the Presumption of Patent Validity and the Deference That Courts Owe to PTO Patentability Determinations 17

II. Review Is Warranted Because the Standard for Patenting Scientific Advances Is an Extraordinarily Important Issue 23

Conclusion 29

TABLE OF CONTENTS (continued)

The following items appear in the separately bound appendix to the petition:

A. Majority and dissenting opinions in the court of appeals (July 9, 2007) 1a

B. First post-trial ruling of the district court (Sept. 15, 2004) 93a

C. Second post-trial ruling of the district court (Dec. 14, 2004) 122a

D. Order of the court of appeals denying rehearing (Sept. 4, 2007) 135a

E. PTO notice of intent to issue first reexamination certificate for the '681 patent (Jan. 11, 2000) 138a

F. PTO notice of intent to issue second reexamination certificate for the '681 patent (Dec. 29, 2006) 146a

G. PTO notice of intent to issue reexamination certificate for the '553 patent (Dec. 15, 2006) 158a

TABLE OF AUTHORITIES

Cases **Pages**

Abbott Labs. v. Syntron Bioresearch, Inc.,
334 F.3d 1343 (Fed. Cir. 2003) 19

Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.,
725 F.2d 1350 (Fed. Cir. 1984) 18, 19

Chicago Rawhide Mfg. Co. v. Crane Packing Co.,
523 F.2d 452 (7th Cir. 1975) 18

Cohn v. United States Corset Co.,
93 U.S. 366 (1876) 25

Dickinson v. Zurko,
527 U.S. 150 (1999) 17, 20

Graham v. John Deere Co.,
383 U.S. 1 (1966) 24, 27

Kahn v. Gen. Motors Corp.,
135 F.3d 1472 (Fed. Cir. 1998) 19

KSR Int'l Co. v. Teleflex Inc.,
127 S. Ct. 1727 (2007) 21, 26, 27, 28

Mendenhall v. Cedarapids, Inc.,
5 F.3d 1557 (Fed. Cir. 1993) 19

Metabolite Labs., Inc. v.
Lab. Corp. of Am. Holdings,
370 F.3d 1354 (Fed. Cir. 2004) 19

Minn. Min. & Mfg. Co. v.
Johnson & Johnson Orthopaedics, Inc.,
976 F.2d 1559 (Fed. Cir. 1992) 19

Parks v. Booth,
102 U.S. 96 (1880) 18

TABLE OF AUTHORITIES (continued)

Cases (continued) **Pages**

PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,
No. 02–148 GMS (D. Del.),
2004 WL 2127192 (Sept. 15, 2004),
2004 WL 2898061 (Dec. 14, 2004),
aff'd in part, rev'd in part,
491 F.3d 1342 (Fed. Cir. 2007) ..... 1, *passim*

Purdue Pharma L.P. v. Faulding, Inc.,
230 F.3d 1320 (Fed. Cir. 2000) 20

Radio Corp. of Am. v. Radio Eng'g Labs., Inc.,
293 U.S. 1 (1934) 18

SIBIA Neurosciences, Inc. v.
Cadus Pharm. Corp.,
225 F.3d 1349 (Fed. Cir. 2000) 19

United States v. Adams,
383 U.S. 39 (1966) 27, 28

Uniroyal, Inc. v. Rudkin-Wiley Corp.,
837 F.2d 1044 (Fed. Cir. 1988) 19

Z4 Techs., Inc. v. Microsoft Corp.,
___ F.3d ____, No. 2006-1638, 2007 WL
3407175 (Fed. Cir. Nov. 16, 2007) 20

Constitutional Provisions and Statutes

U.S. CONST. art. I, § 8, cl. 8 29

28 U.S.C. § 1254(1) 1

28 U.S.C. § 1331 11

28 U.S.C. § 1338 11

TABLE OF AUTHORITIES (continued)

Constitutional Provisions and Statutes (continued) **Pages**

35 U.S.C. § 103(a) 2, 24, 25, 28
35 U.S.C. § 271(b) 14
35 U.S.C. § 271(c) 14
35 U.S.C. § 282 ..... 1, 18
35 U.S.C. §§ 301 *et seq.* 8

Other Authorities

DONALD S. CHISUM, CHISUM ON PATENTS § 5.06[2][b] (2007) 18
MANUAL OF PATENT EXAMINING PROCEDURE § 2270.01 (8th ed. 2001, rev. 2006) 23
PLI Patent Blog, <www.pli.edu/patentcenter/?view=plink&id=61&poll=currentResults&pID=42> (July 10, 2007) 22
The Patent Prospector, <www.patenthawk.com/blog/2007/07/obviousness_vampire_1.html> (July 9, 2007) 22

PETITION FOR A WRIT OF CERTIORARI

PharmaStem Therapeutics, Inc. ("PharmaStem") respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The majority and dissenting opinions of the court of appeals are reported at 491 F.3d 1342 and reprinted at App. 1a–92a. The opinions of the district court resolving the parties' post-trial motions are not officially reported, but are available at 2004 WL 2127192 and 2004 WL 2898061 and are reprinted at App. 93a–134a. The actions by the United States Patent and Trademark Office ("PTO") confirming the validity of the patents-in-suit on reexamination also are not officially reported, but are reprinted at App. 138a–172a.

JURISDICTION

The court of appeals filed its opinion on July 9, 2007. It denied PharmaStem's timely petition for rehearing and rehearing en banc on September 4, 2007. On November 26, 2007, Chief Justice Roberts extended the time for filing this petition to January 2, 2008. No. 07A437. PharmaStem invokes this Court's jurisdiction under 28 U.S.C. § 1254(1).

PERTINENT STATUTES

35 U.S.C. § 282 provides, in relevant part:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form)

> shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent on an invalid claim. . . .

35 U.S.C. § 103(a) provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

This petition raises the proper scope of deference to patentability determinations by the PTO and the proper standard for evaluating the obviousness or nonobviousness of advances in biomedicine.

The patents in this case involve collecting and freezing umbilical cord blood and then thawing and transfusing it into a patient in order to reconstitute the patient's immune system. In five examination and reexamination proceedings over the years, the PTO has repeatedly affirmed and confirmed the validity of the claims. At trial, a unanimous jury agreed that the claims asserted in this case were valid, and the district court upheld that verdict.

By a two-to-one vote, however, a panel of the Court of Appeals for the Federal Circuit reached the opposite result and has invalidated all the asserted claims. As discussed below, the court of appeals failed to give proper weight to the statutory presumption of validity and failed to accord proper deference to the PTO's expertise. The court of appeals also misapplied the law when it found the claims obvious as a matter of law based on a published but unproven and discounted hypothesis that cord blood may contain stem cells.

A. The Patented Inventions, Their Advancement Over the Prior Art, and the Industry They Have Spawned

1. PharmaStem is the holder of reexamined U.S. Patents 5,004,681 ("the '681 patent") and 5,192,553 ("the '553 patent"), which issued in 1991 and 1993, respectively, to inventors Edward Boyse, Hal Broxmeyer, and Gordon Douglas. The two patents describe how to isolate and preserve hematopoietic stem cells from the blood of a newborn baby's umbilical cord or placenta, and how to use those stem cells to treat patients whose immune systems have been compromised. Although the volume of cord blood is small, the inventors found that it can be a rich source of highly potent stem cells that can be used therapeutically. After transfusion into a patient, the stem cells migrate to the bone marrow, cause it to resume normal cell production, and ultimately reconstitute the body's immune system.

The '681 patent claims compositions of cryopreserved stem cells. Claim 1 is illustrative:

> A cryopreserved therapeutic composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells.

The '553 patent covers methods of producing such compositions and using them in therapeutic transplants. Claim 13 is illustrative:

> A method for hematopoietic or immune reconstitution of a human comprising:
>
> (a) isolating human neonatal or fetal blood components containing hematopoietic stem cells;
>
> (b) cryopreserving the blood components;
>
> (c) thawing the blood components; and
>
> (d) introducing the blood components into a suitable human host, such that the hematopoietic stem cells are viable and can proliferate with the host.

2. The inventors named in the patents-in-suit undisputedly pioneered the use of cord blood for immune system reconstitution in the mid-1980s and achieved the world's first successful cord blood trans-

plant in 1988. [A3458–59[1]] They were the first to discover that cord blood transplantation was practical and effective, and their achievements were surprising and contrary to prevailing views in the field.

Before the invention, bone marrow was the standard tissue used in transplant procedures. The medical community treated cord blood as waste to be discarded after birth. [A3408] Although a few scientists had hypothesized that cord blood might contain hematopoietic stem cells, there was, as the district court observed, "tremendous skepticism in the transplant field regarding the use of cord blood as a transplant tissue." [App. 99a] That skepticism was reflected in scientific literature that had taught away from using cord blood.

To begin with, none of the prior art offered conclusive proof that stem cells were actually present in cord blood. [A4019–20] Moreover, the literature suggested, based on colony-forming assays, that if stem cells were present in cord blood at all, they were not present in sufficient quantities to carry out a successful transplant and reconstitute an immune system. [A3761–62] Pooling cord blood samples from multiple sources was not viewed as a viable approach either. [App. 153a, 154a] Another team had failed in an attempt to use noncryopreserved cord blood from multiple donors. [A13354–57] Studies also had shown poor recovery of precursor cells when cord blood was thawed after cryopreservation. [A13348]

Furthermore, regardless of any hypothesis that stem cells might be present in cord blood, none of the

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[1] Citations in this format refer to the joint appendix in the court of appeals.

prior art taught how to perform a transplant using cord blood and achieve successful hematopoietic reconstitution. Such enablement was critical because transplant therapy is extremely risky. Before a transplant, doctors use high-dose radiation to destroy the diseased cells in the patient's immune system. This ensures that the patient's diseased or leukemic cells cannot continue to proliferate, but it also renders the patient's life completely dependent on the transfused donor tissue. Reliability and predictability are thus critical to transplant therapy. [A3485–87]

In short, although there was a long-felt need for alternative sources of stem cells for transplantation, cord blood was not seen as a promising source. The inventors proceeded to defy the prevailing wisdom, to prove that cryopreserved cord blood was a viable source of hematopoietic stem cells, and to enable successful transplantation of such cells in practice.

3. As respondents acknowledged at trial, the inventors' "achievement[s] began a new era in stem cell transplantation." [A3825; A13265–66] The inventors established the first company focusing on cord blood transplantation (Biocyte, Inc., the predecessor of PharmaStem), achieved the first successful transplant, and opened the world's first cord blood bank. Their work became the foundation of a new industry and has saved thousands of lives. [A3723]

After the inventors' trailblazing work, respondents and others entered the field on their coattails, establishing companies that collect, cryopreserve and store umbilical cord blood for a fee. A business plan for a ViaCell subsidiary candidly admitted that "[c]ross country skiing behind the trail blazer con-

serves energy and resources." [A13986–87] It also recognized that the inventors were "core researchers" in the field. [*Id.*] Twenty companies have licensed PharmaStem's patents, reflecting widespread recognition of the novelty and nonobviousness of the patented methods and compositions. Respondents are the only cord blood banks that have refused to license the patents.

B. The PTO's Issuance of the Patents and Its Repeated Confirmation of Their Validity in Later Reexaminations

The PTO has repeatedly considered the validity of the patents-in-suit since the inventors filed their initial application 20 years ago. In every case, the PTO has upheld the validity of the claims asserted in this lawsuit. Indeed, the PTO has specifically and repeatedly found the claims valid over the key prior-art references on which respondents have relied in alleging invalidity as a defense to infringement.

1. The inventors filed the application that led to the '681 patent in November 1987. After over three years of examination, the patent issued in April 1991. The PTO found the claims patentable over dozens of references, including articles by Ende, Knudtzon and Prindull that respondents have cited as invalidating art in this lawsuit.

The '553 patent is a continuation-in-part of the '681 patent. It issued in March 1993 after over four years of examination. The examiner again considered scores of prior-art references, including works by Ende, Knudtzon and Prindull.

2. The Patent Act allows any person to ask the PTO to reconsider the validity of any patent over particular prior art patents or publications. If the PTO finds a substantial new question of patentability, it reexamines the claims and determines whether they should be canceled, confirmed or issued in amended form. *See* 35 U.S.C. §§ 301 *et seq.*

In August 1993, respondent Cryo-Cell requested that the PTO reexamine the '681 patent, contending (among other things) that references by Koike, Douay, Ende, Knudtzon and Prindull rendered the claims invalid. The PTO granted the request and reconsidered the validity of the patent for six years. Finally, in April 2000, the PTO issued a reexamination certificate confirming the validity of one claim intact and reissuing another four (including two asserted in this lawsuit) in amended form.

The reexaminer, who was not the same examiner who originally approved the patents, found that Koike and others had "merely theorized on the presence of stem cells" and no one had "demonstrated the presence of stem cells in the umbilical cord blood." [App. 143a] The reexaminer further determined that only one reference (Ende) "taught a composition which could have contained an amount of viable human neonatal or fetal stem cells sufficient to effect hematopoietic reconstitution," and that Ende did not teach "treatment [that would] result in hematopoietic reconstitution." [App. 142a] Accordingly, one of ordinary skill in the art "would have had no expectation that the hematopoietic reconstitution of a human adult could have been performed" using stem cells and "would have had no motivation to cryopreserve the cord blood." [*Id.*]

3. In June 2004, the '681 patent again went into reexamination proceedings. Again the PTO reconsidered validity over the Koike, Douay, Ende, Knudtzon and Prindull references. And again the reexaminers (this time a panel of three examiners from the more experienced reexamination unit) upheld the claims as previously amended. The second reexamination certificate ultimately issued in June 2007 based on a December 2006 office action.

As to obviousness, the reexaminers found that Koike "fail[ed] to disclose or suggest cryopreserving stem cells in whole blood as required by the . . . claims." [App. 154a] Koike did contain a "suggestion" that "pluripotent" and "progenitor" cells (which are not stem cells) are present in cord blood and "may be useful as one of the sources of hematopoietic progenitor cells for marrow transplantation." [*Id.*] But that "suggestion would not have been enabled at the time of the instant invention": Koike at most suggested that "large amounts of cord blood" would be necessary, requiring "the pooling of at least seven different cord samples from different mothers," which "would be prohibitive." [*Id.*] The reexaminers also found that "the state of the prior art at the time of the instant invention . . . concerning fetal stem cell reconstitution was insufficient to enable the Koike suggestion of employing cryopreserved fetal cord blood." [*Id.*] The reexaminers further agreed that PharmaStem's "total evidence of secondary considerations (evidence of copying, licensing and commercial success) weigh[ed] strongly toward the nonobviousness of the instantly claimed invention." [App. 155a]

4. At the same time, the PTO reexamined the '553 patent, reevaluating its validity in light of

Koike, Douay, Ende, Knudtzon, Prindull and other references. In a December 2006 ruling, the reexaminers (again a team of three) confirmed that the claims of the '553 patent at issue in this lawsuit were neither anticipated nor obvious. A reexamination certificate is expected to issue soon.

As to obviousness, the reexaminers found that Koike had suggested that cord blood contained pluripotent and progenitor cells in comparable amounts to bone marrow, indicating that large amounts of cord blood would be required for successful reconstitution. In contrast, the inventors' studies "established that cord blood contained a substantially higher [level of] progenitor cells," that stem cells from cord blood were more capable of contributing to reconstitution than bone marrow stem cells, and that "progenitor and stem cells in cord blood were in fact effective in achieving hematopoietic reconstitution" at certain volumes and cell doses achievable in humans. [App. 165a–166a] The reexaminers also found that Ende failed to achieve long term engraftment and survival of a patient and did not provide a reasonable expectation of success in using cord blood for reconstitution. [App. 166a] They also relied on evidence of copying, licensing, market acquiescence and commercial success in confirming the claims. [App. 166a–167a][2]

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[2] The PTO confirmed the validity of claims 13–54 and 57–64. Claims 1–12 and 55–56 were canceled during the reexamination. The claims at issue in this litigation were all confirmed.

C. The Jury's Findings That the Claims Are Valid, the District Court's Affirmation of That Finding, and the Federal Circuit's Split Decision Reversing and Invalidating the Claims

1. In February 2002, PharmaStem filed this lawsuit in the District Court for the District of Delaware. The trial court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). PharmaStem asserted infringement of claims 1 and 2 of the '681 patent and claims 13, 19, 47, 53 and 57 of the '553 patent.

The parties tried the case to an eight-person jury in October 2003. After three weeks of trial, the jury returned a unanimous verdict for PharmaStem, resulting in a judgment totaling over $7.1 million. In addition to finding willful infringement, the jury found that respondents had failed to carry their burden of proving that the asserted claims were anticipated or obvious to a person of ordinary skill in the art. The jury also rejected respondents' other validity defenses, their accusation of inequitable conduct during patent prosecution, and ViaCell's antitrust counterclaim. [A35–42]

2. In September 2004, the district court entered its first order addressing the parties' post-trial motions. It upheld the jury's validity verdicts, but it granted judgment as a matter of law ("JMOL") of non-infringement of the '553 patent and it ordered a new trial as to infringement of the '681 patent.

As to obviousness, the district court found that "PharmaStem proffered ample evidence to support the jury's verdict" and the underlying conclusion that "those in the field of hematopoietic reconstitution

would not have expected cord blood to be a successful transplant tissue":

> At trial, PharmaStem presented testimony that there were problems associated with transplant tissues used prior to the Patents-In-Suit. . . . There was also tremendous skepticism in the transplant field regarding the use of cord blood as a transplant tissue . . . and the references ViaCell asserts (namely Koike, Knudtzon and Vidal) did not overcome this skepticism . . . . Finally, testimony established that those in the field of transplantation were surprised at the result of the first cord blood transplant conducted by the inventors of the Patents-In-Suit.

[App. 99a–100a (record citations omitted)]

The district court further noted that "[t]he jury also received an abundance of evidence to support the secondary considerations of long felt need, commercial success, failure of others, copying, and unexpected results." [App. 100a (record citations omitted)] It also recognized that the jury was entitled to consider the fact that the PTO had considered the prior art on which respondents relied when it examined (and, in the case of the '681 patent, reexamined) the claims. [*Id.*]

The district court proceeded to hold that substantial evidence supported the jury's finding that Koike did not anticipate the claims. [App. 101a–103a] It also rejected respondents' contention that the claims were indefinite. [App. 103a–105a] It likewise denied respondents' new trial motion on

inventorship and inequitable conduct issues. [App. *111a–115a] The district court granted JMOL of* non-infringement of the '553 patent, however, and it granted a new trial on infringement of the '681 patent.[3]

3. In December 2004, the district court revised its decision in response to respondents' motion for partial reconsideration. The court did not amend its conclusions regarding the validity of the patents or infringement of the '553 patent. It held, however, that respondents were entitled to JMOL, not a new trial, as to infringement of the '681 patent. [App. 122a–131a]

4. The parties then cross-appealed to the Federal Circuit. By a 2–1 vote, the panel held all the asserted claims invalid for obviousness—notwithstanding the jury's verdict and the PTO's confirmation of the patents' validity both before trial and in the interim while the appeal was pending.[4]

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[3] As to the '553 patent, the district court found that respondents did not perform the entire claimed method of reconstitution by themselves and that PharmaStem did not prove respondents sold or offered to sell a component product used in that process. According to the court, even though respondents sold the services of collecting and cryopreserving blood components, they did not infringe because they did not sell the blood components themselves. [App. 106a–111a] As to the '681 patent, the court concluded that in retrospect it should not have permitted PharmaStem's infringement expert to testify. [App. 115a–119a]

[4] By the same 2–1 vote, the panel also affirmed the grant of JMOL of non-infringement. The majority agreed with the district court that PharmaStem did not show that any of respondents' cord blood contained stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult," as required by the asserted claims of the '681 patent. [App. 13a–

a. Despite the extensive evidence that those skilled in the art believed transplanting cord blood to be hopeless, the majority began its obviousness analysis by assuming that skilled artisans were motivated to transplant cord blood in order to reconstitute immune systems. [App. 36a] On that assumption, the majority viewed the critical question as "whether the prior art would have given rise to a reasonable expectation of success in creating the process claimed in the '553 patent and the composition claimed in the '681 patent." [*Id.*]

Next, although both sides' experts had agreed that there previously had been no conclusive proof that stem cells were present in cord blood, the majority concluded that it was appropriate to infer the presence of such stem cells. [App. 37a–44a] The majority then leapt to the further conclusion that the inventors had merely confirmed what had been suspected before. Such efforts, the majority said, were good science, but were not patentable as an invention. [App. 44a–45a]

In so holding, the majority ignored the claim language. The claimed process and composition required more than just the presence of stem cells in cord blood. The claims of the '681 patent required

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25a] It also held that PharmaStem did not prove contributory infringement of the '553 patent because respondents only sold services to families of newborn infants and did not sell the cord blood units themselves. According to the majority, providing a service can result in liability for inducing infringement under 35 U.S.C. § 271(b), but contributory infringement under 35 U.S.C. § 271(c) requires sale of an actual product. [App. 26a–34a]

Although PharmaStem strongly disagrees with the noninfringement rulings, this petition focuses on the validity issues.

that stem cells be "present in an amount sufficient to effect hematopoietic reconstitution of a human adult" and the claims of the '553 patent required that the method accomplish "hematopoietic or immune reconstitution of a human." Thus, the question was not whether a skilled artisan would have thought that stem cells might be present in cord blood, but whether skilled artisans would have thought that those stem cells could be effectively transplanted and reconstitute the patient's hematopoietic system. The majority ignored the wealth of evidence (cited by both the district court and the PTO) that scientists in the field believed that cord blood was not a viable, practical source of sufficient high-potency stem cells.

The majority next proceeded to discount the objective evidence of nonobviousness on which the many prior findings of validity had relied. The majority minimized the evidence showing that the inventors were widely recognized as pioneers (even by respondents); it criticized PharmaStem's expert's testimony that the inventors' work was greeted with surprise; and it dismissed the evidence that others began their experiments only after reviewing the inventors' work. [App. 47a–49a] The majority ignored the other evidence of long-felt need, commercial success, failure of others, copying, unexpected results, licensing and market acquiescence that the jury, district court and PTO had found persuasive.

Finally, although recognizing that the issue of obviousness was a "difficult question" [App. 51a], the majority declined to defer to the repeated contrary conclusions of the numerous PTO examiners. It simply disagreed with the examiner who issued the first reexamination certificate for the '681 patent.

[App. 49a–51a] Moreover, although the panel held the appeal for over a year while the PTO considered two more reexamination petitions, the majority wholly ignored the PTO's December 2006 confirmation of both patents over the same art and arguments.

b. Judge Newman dissented at length and with vigor. Although she also addressed infringement, Judge Newman focused primarily on validity. She summarized her position and objections to the majority's treatment in her introduction:

> The undisputed evidence at trial was that these long-sought life-saving inventions were achieved amid general scientific skepticism .... The discoveries of these inventors were met with universal acclaim and widespread utilization, including the founding of many commercial enterprises, all of which are reported to have licensed the patents except these defendants. Unimpressed by these considerations, my colleagues on this panel now reconstruct these inventions by selection and inference, with perfect hindsight of the discoveries. The evidence at trial was that this achievement eluded persons working in the field, despite speculation concerning its potential and recognition of its value if it could actually be achieved; despite the powerful interest in such a life-saving advance. Instead, my colleagues simply reweigh selectively extracted evidence, ignore the actual peer response and acclaim at the time these inventions were made, and decide that this

> long-sought advance would have been obvious to this court.

[App. 54a]

Judge Newman particularly excoriated the majority's refusal to credit "not only the scientific experts who testified at the trial, but also the PTO examiners who conducted the three reexaminations." Citing *Dickinson v. Zurko*, 527 U.S. 150 (1999), where this Court reminded the Federal Circuit of its obligation to defer to the PTO's expertise, she noted:

> My colleagues do not explain where the PTO went wrong; instead, they rearrange the past, criticize the acclaim heaped on these inventors, and propose that if the people in this field knew what this court knows, they would not have been so impressed.

[App. 56a]

5. PharmaStem filed a timely petition for rehearing and rehearing en banc, but the Federal Circuit denied the petition without comment. [App. 135a–136a]

This petition for a writ of certiorari followed.

ARGUMENT FOR GRANTING THE WRIT

I. Review Is Warranted So That This Court Can Clarify the Presumption of Patent Validity and the Deference That Courts Owe to PTO Patentability Determinations

Judges have long deferred to the expertise of PTO examiners and recognized that courts should presume the validity of patents issued by the PTO. This

Court recognized the presumption of validity back in 1880 and reaffirmed it in 1934. *See Parks v. Booth*, 102 U.S. 96, 99 (1880); *Radio Corp. of Am. v. Radio Eng'g Labs., Inc.*, 293 U.S. 1, 2 (1934). Congress eventually codified the presumption in the Patent Act of 1952. *See* 35 U.S.C. § 282.

Since 1952, however, the lower courts have struggled to determine what the presumption means and how it applies. The struggle became apparent long before the Federal Circuit received exclusive jurisdiction over appeals in patent infringement cases in 1982. Some courts described the presumption as strictly a procedural device that placed the burden of production and persuasion on the party challenging a patent's validity. Others viewed it as having a substantive component in the sense that it strengthened or weakened depending on whether the Patent Office had considered the prior art raised in the district court litigation. *See generally* DONALD S. CHISUM, CHISUM ON PATENTS § 5.06[2][b] (2007).

In *Chicago Rawhide Manufacturing Co. v. Crane Packing Co.*, 523 F.2d 452 (7th Cir. 1975), then-Judge Stevens sought to reconcile the two views. In his view, the presumption of validity had two aspects, one (purely procedural) that remains constant and one (founded in deference to examiners' technical expertise) that is variable in the sense that it is harder or easier for a challenger to sustain its burden of proving invalidity depending on whether the Patent Office had previously considered the prior art on which the challenger raises. *Id.* at 457–58.

Early in its history, the Federal Circuit adopted a similar position. In *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, the court reasoned that the

presumption of validity and the requirement that a challenger establish invalidity by clear and convincing evidence always apply, but that a challenger's burden in attacking validity is easier to discharge when it raises art not considered by the PTO and more difficult to discharge when it relies on references that the PTO did consider. 725 F.2d 1350, 1359–60 (Fed. Cir. 1984). The Federal Circuit has echoed these principles from time to time in some of its later cases. *See, e.g., Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings,* 370 F.3d 1354, 1368 (Fed. Cir. 2004); *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1357 (Fed. Cir. 2003); *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1355–56 (Fed. Cir. 2000); *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1480 (Fed. Cir. 1998).

In other cases, however, the Federal Circuit has stated the law somewhat differently. *See, e.g., Minn. Min. & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1572 (Fed. Cir. 1992) (where the PTO has considered a piece of prior art, a court owes "some deference" to the agency's decision); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050 (Fed. Cir. 1988) (reliance on art not considered by PTO facilitates meeting burden of proving invalidity "when that art is more pertinent than the art considered by the PTO" (citation omitted)).

The Federal Circuit has also given conflicting signals on how juries should be instructed. *Compare Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557, 1564 (Fed. Cir. 1993) (appropriate to instruct that "[b]ecause the deference to be given the Patent Office's determination is related to the evidence it had before it, you should consider the evidence presented to the

Patent Office during the reissue application process, compare it with the evidence you have heard in this case, and then determine what weight to give the Patent Office's determinations"), *with Z4 Techs., Inc. v. Microsoft Corp.*, ___ F.3d ____, No. 2006-1638, 2007 WL 3407175, at *22–*23 (Fed. Cir. Nov. 16, 2007) (affirming refusal to give jury instruction that the attacker's "burden is more easily carried when the references on which the assertion is based were not directly considered by the examiner during the prosecution" (citation omitted)).

For its part, this Court has not squarely addressed the presumption of validity in over 70 years, and it has never addressed whether the PTO is owed especial deference in cases of reexamined patents.

In *Dickinson v. Zurko*, this Court reversed the Federal Circuit and held that the Administrative Procedure Act's standards of judicial review govern when the Federal Circuit reviews patentability determinations by the PTO. Such review is highly deferential: the "court reviews an agency's reasoning to determine whether it is 'arbitrary' or 'capricious,' or, if bound up with a record-based factual conclusion, to determine whether it is supported by 'substantial evidence.'" 527 U.S. at 164 (citation omitted).

Shortly after *Zurko*, however, the Federal Circuit limited this Court's holding to direct appeals of PTO determinations, holding that it had "no application" where, as here, accused infringers indirectly challenge such findings in defending against infringement actions filed in district court. *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1329 (Fed. Cir. 2000). Although both the Administrative Procedure Act standard of review and the statutory presump-

tion of validity are rooted in the technical expertise of the PTO, the deference the Federal Circuit now accords to PTO findings varies significantly depending on which path a case takes to that court.

This Court's decision last Term in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), did not resolve the question. *KSR* dealt primarily with the problem of determining when a combination of references renders a patent obvious. In passing, the Court observed that the presumption of validity is founded on the expertise of the PTO, but it declined to decide whether the presumption is voided or diminished when the allegedly invalidating prior art was not presented to the PTO:

> We need not reach the question whether the failure to disclose Asano during the prosecution of Englegau voids the presumption of validity given to issued patents, for claim 4 is obvious despite the presumption. We nevertheless think it appropriate to note that the rationale underlying the presumption—that the PTO, in its expertise, has approved the claim—seems much diminished here.

Id. at 1745.

This case now raises the complementary question of whether the presumption of validity strengthens where, as here, the PTO specifically finds claims patentable over particular prior art. As shown above, the PTO carefully scrutinized the prior art on which the majority below relied in declaring the claims invalid for obviousness. The PTO not only issued the claims, but reissued them multiple times

after reexaminations, rejecting the very obviousness arguments that respondents made in this litigation. Although briefly acknowledging "the deference that is due to a qualified government agency presumed to have done its job" [App. 49a], the majority proceeded to substitute its nonexpert view for those of numerous examiners—and the views of a unanimous jury and trial judge who heard the evidence first-hand.

The issues raised by this petition are extraordinarily important. The presumption of validity is fundamental to patent law, and validity is litigated in almost every patent case. Litigants and courts need to know how much deference to give to determinations of validity by the PTO and whether the presumption of validity has a substantive component as well as a procedural one. In particular, they need to know whether the presumption of validity is stronger where the PTO has specifically considered a particular reference and weaker where it has not.

Notably, the patent bar has recognized the importance of the issues raised by this petition. For example, bloggers have criticized the Federal Circuit majority for exercising "carte blanche" and reaching its decision of obviousness "based on its [own] analysis of the prior art." *See* The Patent Prospector, <www.patenthawk.com/blog/2007/07/obviousness_vampire_1.html> (July 9, 2007); PLI Patent Blog, <www.pli.edu/patentcenter/?view=plink&id=61&poll=currentResults&pID=42> (July 10, 2007). Commentators have also remarked on the pointlessness of multiple PTO reexaminations if the Federal Circuit can conduct its own reexamination and invalidate for obviousness. PLI Patent Blog, *supra* (urging this Court to "come to the rescue because as long as

we are going to have a reexamination procedure it might as well actually mean something").

This case is a particularly good vehicle to decide the questions presented because it involves patent claims that survived reexaminations as well as initial examination. The point of a reexamination is to have a panel of expert examiners reevaluate claims in light of particular prior art that was not considered or was not fully considered during the initial examination. *See* MANUAL OF PATENT EXAMINING PROCEDURE § 2270.01 (8th ed. 2001, rev. 2006). Patentees and accused infringers often initiate reexaminations so that the PTO can apply its expertise to additional prior art, and trial courts often stay litigation in light of pending reexaminations. In seeking reexamination, parties assume that the PTO's decision will receive deference in the courts, but no one is clear on how much deference. Accepting review would clarify the law for the benefit of everyone.

II. Review Is Warranted Because the Standard for Patenting Scientific Advances Is an Extraordinarily Important Issue

The Federal Circuit's decision sets a standard for patentability that threatens many inventions in the biotechnology and pharmaceutical industries, if not all of science. According to the court of appeals, the mere hypothesis that a fact may be true precludes later patenting of a technique that builds on that fact, even where the technique was never enabled, the hypothesis had not been confirmed, and those skilled in the art had rejected the approach. This Court has never imposed such a standard, and as Judge Newman recognized in dissent, the decision

below is based on a fundamental "misperception of the scientific process." [App. 80a]

The concept that a patent may not issue if the subject is obvious dates back to at least 1850, although the term "obvious" first appeared in the Patent Act in 1952. By statute, the obviousness or nonobviousness of a patent claim turns on the state of the art at the time the invention was made. 35 U.S.C. § 103(a). Whether a claim is obvious does *not* depend on whether an invention required a "flash of creative genius" as opposed to "merely the skill of the calling." *Graham v. John Deere Co.*, 383 U.S. 1, 15 & n.7 (1966) (citation omitted). Congress abolished any requirement for a "flash of creative genius" by adopting the final sentence of Section 103(a): "Patentability shall not be negatived by the manner in which the invention was made."

The decision below undermines *Graham* and contravenes Section 103(a) because it effectively revives the discredited "flash of creative genius" test. The majority below deemed PharmaStem's patents "not inventive in nature" but simply "proof, through laboratory work, that fetal blood contains large numbers of stem cells." [App. 44a, 47a] In fact, the inventors were the first not only to prove conclusively that stem cells were present in cord blood, but also the first to discover and demonstrate that those cells were potent enough and present in large enough numbers that they could be cryogenically preserved and successfully transplanted to reconstitute a patient's immune system.

If this breakthrough in using cord blood was not "inventive," it is difficult to imagine many biotechnological or pharmaceutical achievements that would

be patentable. Most discoveries made by biotechnology and pharmaceutical companies are rooted in diligent application of the scientific method. As a former scientist, Judge Newman appreciated this in a way that her colleagues could not.[5]

Scientists commonly posit theories or hypotheses based on what is already known in the art. But mere hypotheses have never constituted invalidating prior art, for they are theoretical abstractions that have not been enabled and are not in anyone's possession. As this Court recognized over 140 years ago, prior art is "insufficient to invalidate [a] patent" unless it "exhibit[s] the later patented invention in such a full and intelligible manner as to enable persons skilled in the art to which the invention is related to comprehend it without assistance from the patent, or to make it, or repeat the process claimed." *Cohn v. United States Corset Co.*, 93 U.S. 366, 370 (1876). Ultimate proof of a conjecture is often the subject of arduous trial and error, but Congress has declared that inventions made by persistent and methodical efforts are just as patentable as those derived from flashes of genius. *See* 35 U.S.C. § 103(a).

Of course, patents do not issue simply because someone was the first to do something. As Section 103(a) recognizes, the PTO and the courts must consider what the prior art taught to those of ordinary skill in the art at the time the invention was made. Just last Term, however, this Court rejected "rigid," "formalistic" approaches to the obviousness analysis,

---

[5] Judge Newman has a Ph.D. in chemistry and formerly worked as a research scientist. The two judges in the majority below (Judges Bryson and Prost) were not scientists.

reaffirming its own precedents that taught to apply a more flexible approach. *KSR*, 127 S. Ct. at 1741. The Court in *KSR* certainly did not hold or suggest that the mere existence of an untested hypothesis in the prior art *ipso facto* renders an invention obvious.

In fact, the decision below is in tension with *KSR* for a number of reasons. First, this Court warned of the danger of "falling prey to hindsight bias" in analyzing obviousness. *KSR*, 127 S. Ct. at 1742. Yet that is exactly what occurred here, as two appellate judges re-reviewed the record evidence and came to a conclusion at odds with numerous patent examiners, a unanimous jury and the district court. As Judge Newman put it in dissent, the majority "reconstruct[ed]" the claimed inventions "by selection and inference, with perfect hindsight of the discoveries," instead of examining the patents in the context of the knowledge at the time the inventions were made, as required by this Court's precedent. [App. 54a] The majority never explained why no one else had pursued the patented technique if it had been so obvious from the prior art.

Second, in *KSR* this Court observed that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." 127 S. Ct. at 1740. Here, as discussed above, the prior art taught away from the idea that a small volume of cord blood harvested from one newborn could contain enough stem cells to reconstitute an immune system, and it taught away from the idea that cord blood could be cryopreserved. The majority below brushed aside the "tremendous skepticism in the transplant field regarding the use of cord blood as a

transplant tissue" even though that was one of the key reasons that the district court upheld the jury's verdict of nonobviousness. [App. 99a]

Third, in *KSR* this Court reaffirmed *Graham*'s guidance that courts should consider "secondary considerations," such as commercial success, long felt but unsolved needs and failure of others, in determining obviousness. 127 S. Ct. at 1739. Again second-guessing the PTO and the district court, the court of appeals gave short shrift to those considerations. It effectively ignored the commercial success of the cord blood industry that the inventors enabled, the acquiescence of most of the industry in taking licenses, and the inventors' success in solving the long-felt need for an alternative to bone marrow for transplant tissue.

The Federal Circuit's decision also conflicts with this Court's analysis in *United States v. Adams*, 383 U.S. 39 (1966), a companion case to *Graham* and a case that the Court reaffirmed in *KSR*, 127 S. Ct. at 1739–40. Adams designed an electrical battery. As this Court observed, "[t]he basic idea of chemical generation of electricity [wa]s, of course, quite old." 383 U.S. at 45. The underlying scientific principles had been the subject of extensive discussion and hypotheses, and "various electrolyte possibilities and many combinations of these elements ha[d] been the object of considerable experiment for almost 175 years." *Id.* Nevertheless, the Court affirmed the validity of the patent. Adams's design had unexpected advantages, and he had defied conventional wisdom by disregarding prior art that taught away from his approach. *Id.* at 51–52. Moreover, "noted experts [had] expressed disbelief" in the invention, and "[s]everal of

the same experts subsequently recognized [its] significance." *Id.* at 52.

Likewise here, although many hypotheses existed and many experiments had been conducted, the prior art taught away from using cord blood as a source for stem cells that could be transplanted to reconstitute immune systems. The inventors ignored that prevailing skepticism, and their results were met with great surprise and acclaim. At a minimum, the PTO, the jury and the district court were entitled to find that their invention was not obvious.

The consequences of the decision below will be severe. By holding that a past hypothesis precludes later patenting regardless of the general rejection of the hypothesis or the acclamation that greets its proof and practical enablement, the Federal Circuit has greatly reduced the incentive for innovation in industries that rely on experimental research.

Hypotheses are cheap; proving a principle and practically enabling a new composition or method are not. The biotechnology and pharmaceutical industries depend heavily upon periods of exclusive rights to recoup their long-term research and development costs. It can take a pharmaceutical company, for example, a decade and hundreds of millions of dollars to develop a product, see it through clinical trials, and obtain Food and Drug Administration approval to market it.

By ignoring the final sentence of Section 103(a) and raising the bar of patentability, the Federal Circuit has greatly reduced the incentive for innovation and disserved the fundamental purpose of the patent system: "To promote the Progress of Science and

useful Arts." U.S. CONST. art. I, § 8, cl. 8. As in *KSR*, review by this Court is needed to reset the law on a proper course.

CONCLUSION

A writ of certiorari should be granted.

Respectfully submitted,

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January 2, 2008

Supreme Court, U.S.
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No. _____

IN THE

Supreme Court of the United States

PHARMASTEM THERAPEUTICS, INC.,
Petitioner,

v.

VIACELL, INC.; CRYO-CELL INTERNATIONAL, INC.; CORCELL, INC.; and CBR SYSTEMS, INC. (formerly known as CORD BLOOD REGISTRY, INC.),
Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

APPENDIX TO PETITION FOR A WRIT OF CERTIORARI

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TABLE OF CONTENTS

A. Majority and dissenting opinions in the court of appeals (July 9, 2007) 1a

B. First post-trial ruling of the district court (Sept. 15, 2004) 93a

C. Second post-trial ruling of the district court (Dec. 14, 2004) 122a

D. Order of the court of appeals denying rehearing (Sept. 4, 2007) 135a

E. PTO notice of intent to issue first reexamination certificate for the '681 patent (Jan. 11, 2000) 138a

F. PTO notice of intent to issue second reexamination certificate for the '681 patent (Dec. 29, 2006) 146a

G. PTO notice of intent to issue reexamination certificate for the '553 patent (Dec. 15, 2006) 158a

APPENDIX A

United States Court of Appeals for the Federal Circuit

05-1490, -1551

PHARMASTEM THERAPEUTICS, INC.,
Plaintiff-Appellant,

v.

VIACELL, INC.,
Defendant-Cross Appellant,

and

CRYO-CELL INTERNATIONAL, INC., CORCELL, INC.,
Defendants-Cross Appellants,

and

CBR SYSTEMS, INC. (formerly known as Cord Blood Registry, Inc.),
Defendant-Cross Appellant,

and

BIRTHCELLS TECHNOLOGY, INC. and BIO-CELL, INC.,
Defendants.

Paul J. Andre, Perkins Coie, LLP, of Menlo Park, California, argued for plaintiff-appellant Pharmastem Therapeutics, Inc. With him on the brief was Lisa Kobialka.

John C. Englander, Goodwin Procter LLP, of Boston, Massachusetts, argued for defendant-cross appellant ViaCell, Inc. With him on the brief were Paul F. Ware, Jr. and Elaine Herrmann Blais. Of counsel on the brief was Richard M. Wyner, of Washington, DC.

James J. Rodgers, Dilworth Paxson LLP, of Philadelphia, Pennsylvania, argued for defendants-cross appellants Cryo-Cell International, Inc., et al. Of counsel was Evelyn H. McConathy, Drinker Biddle & Reath LLP, of Philadelphia, Pennsylvania.

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Appealed from: United States District Court for the District of Delaware

Chief Judge Gregory M. Sleet

United States Court of Appeals for the Federal Circuit

05-1490,-1551

PHARMASTEM THERAPEUTICS, INC.,
Plaintiff-Appellant,

v.

VIACELL, INC.,
Defendant-Cross Appellant,

and

CRYO-CELL INTERNATIONAL, INC., CORCELL, INC.,
Defendants-Cross Appellants,

and

CBR SYSTEMS, INC. (formerly known as Cord Blood Registry, Inc.),
Defendant-Cross Appellant,

and

BIRTHCELLS TECHNOLOGY, INC. and BIO-CELL, INC.,
Defendants.

DECIDED: July 9, 2007

Before NEWMAN, BRYSON, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge BRYSON. Dissenting opinion filed by Circuit Judge NEWMAN.

BRYSON, Circuit Judge.

This patent infringement action was brought by appellant PharmaStem Therapeutics, Inc., in the United States District Court for the District of Delaware. PharmaStem sued six defendants (four of which are appellees before us in this appeal), alleging that the defendants had infringed two patents owned by PharmaStem, U.S. Patent No. B1 5,004,681 ("the '681 patent") and U.S. Patent No. 5,192,553 ("the '553 patent"), a continuation-in-part of the '681 patent. At the conclusion of the trial, the jury returned verdicts for PharmaStem on both patents, finding both patents infringed and not invalid. The jury also rejected the defendants' counterclaims of inequitable conduct and violation of the antitrust laws.

The defendants filed motions for judgment as a matter of law ("JMOL") and a new trial. In response, the district court initially entered an order granting a new trial on the issue of infringement of the '681 patent and JMOL of noninfringement as to the '553 patent. Subsequently, however, the court vacated the new trial order as to the '681 patent and instead entered JMOL of noninfringement as to that patent. The court denied the defendants' JMOL motions with respect to various asserted grounds of patent invalidity. PharmaStem now appeals from

the JMOL orders on infringement, and the defendants cross-appeal from the court's refusal to grant JMOL on invalidity. We affirm the district court's judgment as to the infringement issues. With respect to the counterclaim of invalidity for obviousness, however, we reverse the judgment and direct the entry of judgment for the defendants.

I

The two patents in suit recite compositions and methods relating to a medical procedure for treating persons with compromised blood and immune systems. The treatment is based on the discovery that blood from a newborn infant's umbilical cord is a rich source of a type of stem cells useful for rebuilding an individual's blood and immune system after that system has been compromised by disease or a medical treatment such as chemotherapy.

Stem cells are fundamental (or "immature," or "primitive") cells from which specialized (or "mature") cells derive. Hematopoietic stem cells are stem cells that are ultimately responsible for producing the various specialized cells of the blood and immune (or "hematopoietic") system. Hematopoietic stem cells produce progenitor cells and more hematopoietic stem cells. The progenitor cells, which are less primitive than the stem cells, in turn give rise to the variety of specialized cells that constitute the blood and immune system.

Although hematopoietic stem cells are present in various types of human tissue, they are found in unusually high concentration and potency in

umbilical cord blood. The '681 and '553 patents describe a process for collecting a newborn infant's umbilical cord blood at the time of birth, testing it for suitability for later use, preserving it through cryopreservation, and infusing it into an individual (either the donor or another person, preferably one with a closely matched blood type) whose hematopoietic stem cells have been destroyed. The object of such transplantations is to effect grafting. A successful graft results when the donor's stem cells migrate into the recipient's bone marrow, resulting in the renewed production of normal, specialized blood cells and ultimately the reconstitution of the recipient's entire blood and immune system.

As issued, the '681 patent contained very broad claims. Claim 1 recited a composition comprising "a plurality of viable human neonatal or fetal hematopoietic stem cells derived from the blood [and a] cryopreservative." In reexamination, several of the original claims were cancelled. Claim 1 was amended to read as follows:

> A cryopreserved therapeutic composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells.

Claim 2, which is dependent on claim 1, was amended to recite the composition of claim 1 "which further comprises viable human neonatal or fetal hematopoietic progenitor cells."

Each of the defendants offers a service to families of newborn infants in which blood from the infant's umbilical cord is collected and cryopreserved for possible later use. The defendants represent in their promotional literature that the preserved cord blood may be useful for reconstituting the donor's hematopoietic system in the event that system is damaged or destroyed as a result of disease or other causes. Some of the promotional literature advises that the preserved cord blood may also be useful for treating closely related members of the infant's family.

In the infringement action brought against all six defendants, PharmaStem asserted claims 1 and 2 of the '681 patent, as amended in reexamination, and claims 13, 19, 47, 53, and 57 of the '553 patent. Claims 13, 47, and 57 of the '553 patent are independent claims. Claim 13 provides as follows:

> A method for hematopoietic or immune reconstitution of a human comprising:
>
> (a) isolating human neonatal or fetal blood components containing hematopoietic stem cells;
>
> (b) cryopreserving the blood components;

> (c) thawing the blood components; and
>
> (d) introducing the blood components into a suitable human host, such that the hematopoietic stem cells are viable and can proliferate with the host.

Claim 47 is similar except that it refers to the blood components "containing hematopoietic stem and progenitor cells." Dependent claims 19 and 53 add that the blood components are isolated by collection from an umbilical cord. Independent claim 57 provides as follows:

> A method for hematopoietic or immune reconstitution of a human comprising introducing into the human a composition comprising human neonatal or fetal hematopoietic stem cells derived from the blood, in which the stem cells have been previously cryopreserved.

II

Following the jury's verdict finding infringement of both patents by all four appellants, the district court granted the defendants' JMOL motions and entered a judgment of noninfringement with respect to both patents. The court agreed with the defendants that, in light of the legal theories pressed by PharmaStem at trial, the evidence failed to show that any of the defendants had infringed any of the asserted claims of either patent in suit.

As to infringement of the asserted '681 patent claims, the district court focused on the requirement that the recited compositions contain stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult." To prove infringement, the court explained, PharmaStem was required to adduce evidence that the defendants' cord blood units contained a sufficient supply of stem cells to effect successful reconstitution of an adult. The court concluded that PharmaStem had failed to do so.

In addressing the sufficiency of the evidence on that issue, the trial court first ruled that it should have excluded the trial testimony of Dr. Mary Hendrix, PharmaStem's expert witness on infringement. The court noted that although Dr. Hendrix was "an accomplished stem cell biologist," she based her infringement opinion "entirely on an analysis of the defendants' marketing materials, without ever considering any data regarding the composition of the defendants' cord blood units." The court explained that Dr. Hendrix was not qualified as an expert in marketing or advertising and, in any event, "her so-called analysis of the defendants' marketing materials was well within the jury's common knowledge, common sense and common experience." The court pointed out that Dr. Hendrix's opinion that all of the defendants' cord blood units infringe was based on her conclusion that the defendants' promotional materials "promise stem cells for pediatric and adult transplantation." In that respect, according to the court, "her opinion of infringement is no more than a lay-person's interpretation of the defendants' marketing

materials." The court therefore ruled that her testimony should have been excluded and that "permitting PharmaStem to couch its presentation of this evidence in the form of an expert opinion was an error."

The district court then pointed out that the evidence at trial overwhelmingly indicated that not all units of cord blood obtained from a single individual at birth contain enough stem cells to reconstitute an adult. The court explained that PharmaStem did not attempt to prove by testing or by reference to data collected by the defendants that at least some of the cord blood samples preserved by the defendants satisfied that requirement. Instead, the court noted, PharmaStem adopted the strategy of trying to prove, principally through representations made by the defendants in their marketing materials and other documents, that all of the preserved cord blood samples infringed. As a consequence, the court explained, PharmaStem "presented no evidence to the jury from which it could conclude that any specific cord blood unit or units stored by any of the defendants contained stem cells in a sufficient amount to reconstitute a human adult." Because there was "no legally sufficient evidentiary basis for a reasonable jury to find that all, or any specific number, of the defendants' cord blood units infringe the '681 patent," the court granted the defendants' motion for JMOL as to the '681 patent claims.

As to infringement of the '553 patent, the district court granted the defendants' motions for JMOL because it concluded that PharmaStem had failed to prove that the defendants were guilty of

contributory infringement, which was PharmaStem's theory of liability. Under the court's instructions, the jury was required to answer three questions in the affirmative in order to find that any of the defendants contributorily infringed the '553 patent. Specifically, the jury was required to find (1) that cryopreserved cord blood has no substantial noninfringing uses; (2) that the defendants and transplant physicians were acting in concert or working together to complete the process of infringement of the asserted claims of the '553 patent; and (3) that the defendants contributorily infringed "by selling or offering to sell cryopreserved cord blood that was actually used by a third party in the direct infringement" of the asserted claims. The court held that there was sufficient evidence at trial to support the jury's affirmative answers to the first two questions. With respect to the third question, however, the court held that there was no evidence in the record to support the jury's affirmative answer. The court explained its ruling as follows:

> It is undisputed that the defendants do not own the cord blood units. Rather the units are owned by the clients, or families, and the defendants in turn provide services with respect to the processing and storing of the compositions. Although the defendants charge enrollment, processing, and banking fees with respect to their storage services, they do not sell or offer to sell the cord blood units. Indeed, the record evidence on this issue is clear

> that the defendants sell a service, not cord blood units.

Because the court ruled that liability for contributory infringement "is clearly dependent upon the accused infringer's selling or offering to sell a component of the patented process, here cord blood units," the court held that the jury's verdict could not stand. The court therefore granted JMOL as to the asserted claims of the '553 patent.

Although granting the defendants' motions for JMOL as to infringement, the district court denied their motions for JMOL of invalidity with respect to the asserted claims. As to obviousness, the court ruled that the evidence at trial showed that there were problems associated with the use of other transplant tissues, such as bone marrow and adult blood, and that there was "tremendous skepticism in the transplant field regarding the use of cord blood as a transplant tissue." Although the court stated that a jury could have found from the evidence that the asserted claims would have been obvious, the court ruled that the evidence was sufficient to entitle the jury to conclude that "prior to the inventions of the Patents-In-Suit, those in the field of hematopoietic reconstitution would not have expected cord blood to be a successful transplant tissue."

As to anticipation, the district court again ruled that the evidence was sufficient to support the jury's verdict that the prior art reference on which the defendants relied did not anticipate the asserted claims. The court explained that the jury was entitled to find that the prior art reference did not

prove that there were stem cells in umbilical cord blood, and that the jury could reasonably have concluded that the suggestion of introducing stem cells into a human host was not "a sufficiently enabling disclosure to warrant a finding of anticipation."

Finally, the district court rejected the defendants' argument that the '681 patent was invalid for indefiniteness. The court acknowledged that claim 1 of the '681 patent does not specify a particular number of cells or volume of blood that is required to infringe. Nonetheless, the court concluded that "the record supports that the '681 Patent's claim language is as precise as the subject matter permits." Moreover, the court ruled that the record contained evidence establishing that "a person of skill in the art would have understood what an amount of cord blood stem cells sufficient to effect hematopoietic reconstitution of a human adult means."

PharmaStem has appealed from the portion of the district court's judgment granting JMOL of noninfringement with respect to both patents. The defendants have cross-appealed from the portion of the judgment upholding the jury's verdict that the two patents are not invalid on grounds of anticipation, obviousness, or (in the case of the '681 patent) indefiniteness.

III

With respect to infringement of the '681 patent, the dispute on appeal is a narrow one. The only contested limitation of the asserted claims is the

limitation requiring that the claimed composition contain neonatal or fetal hematopoietic stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult." PharmaStem contends that all of the cord blood samples the defendants have preserved infringe claim 1 of the '681 patent because the evidence at trial was sufficient to show that all those cord blood units contained enough stem cells to effect the hematopoietic reconstitution of a human adult. The defendants contend that PharmaStem failed to prove that any of their cryopreserved samples satisfy that limitation.

As the district court noted, PharmaStem did not attempt to use direct testing or other scientific evidence to prove that any particular cord blood sample or group of samples preserved by any of the defendants contained enough stem cells to reconstitute a human adult. Instead, PharmaStem relied on indirect evidence in the form of advertising and other materials generated by the defendants, scientific evidence relating to stem cell research in general, testimony from representatives of the defendants, and testimony by their own expert witness, Dr. Hendrix. The district court, however, concluded that PharmaStem's evidence did not constitute substantial evidence in support of PharmaStem's theory of infringement.

A

The trial court was correct in ruling that the evidence of the defendants' advertising and other materials did not provide a sufficient basis for a finding of infringement. That evidence consisted of

various statements by each of the defendants that the cord blood samples they preserved could be potentially useful not only for the donor but also for the donor's relatives, including adult relatives.

To be sure, there is no prohibition against using the admissions of a party, whether in the form of marketing materials or otherwise, as evidence in an infringement action; such admissions are entitled to weight along with all other evidence of infringement. In this case, however, while the defendants' statements touted the possible therapeutic uses the cord blood might have for the child and members of the child's family in the future, none of the statements represented that the stem cells in any of the cryopreserved cord blood samples were sufficient in number to effect hematopoietic reconstitution of an adult, as is required by claim 1 of the reexamined '681 patent. Instead, the defendants' statements emphasized the potential therapeutic usefulness of the cord blood in general and referred to future uses of stored blood in adult transplants only as possibilities.

For example, PharmaStem introduced a statement from a website maintained by defendant CBR Systems, Inc., which referred to the number and character of cord blood transplants worldwide as of that time. The statement recited that "umbilical cord blood has been used in more than 2,500 transplants by children and adults. In many cases, the cord blood was used by the baby's sibling. Other transplants have occurred for the newborn himself, the newborn's mother, father, and the newborn's cousin." With respect to its own preserved cord blood

units, CBR stated that it had provided "over two dozen samples for use in transplantation," that most have been used for siblings, but that in one instance the newborn's "cord blood stem cells were transplanted to her mother to treat chronic myelogenous leukemia."

Those statements fall short of proving that any (much less all) of CBR's cord blood samples contained enough stem cells to reconstitute an adult. The first statement simply recited that among the 2500 world-wide transplants, some had been conducted on adults. The second statement reflected that one such adult transfer was attempted with a CBR cord blood sample. Neither statement made any representation whether or to what extent the particular transplants had succeeded in reconstituting the adults' hematopoietic systems. Nor did the specific reference to the one adult transplant represent that the transplant was successful or that only a single unit of cord blood was used in the transplant. Those gaps in the proof are significant, because the evidence showed that as of the time of trial the great majority of all cord blood transplants worldwide had been for the treatment of children. In addition, the evidence showed that in most cases involving adult transplantations, the transplant physicians had used two units of cord blood, not the one unit obtained at the time of a single birth. Uncontradicted evidence at trial showed that two units were used because in most cases the physicians regarded a single unit as insufficient for an adult transplantation.

PharmaStem introduced similar statements from defendant CorCell, Inc. In particular, PharmaStem pointed to a statement in CorCell's promotional literature that if cord blood could be saved, "it would be a perfect match for the donor, but could also provide life saving benefits for siblings, and other family members." Several other statements by CorCell were to the same effect—that cord blood could potentially be of benefit not only to the child but also to other members of the child's family. As in the case of CBR, however, those statements did not constitute representations that single units of CorCell's preserved cord blood would contain a sufficient number of stem cells to reconstitute an adult. PharmaStem notes in passing that one sample of CorCell's preserved cord blood was used in an adult transplantation, but the evidence at trial showed that the adult transplant did not graft and the patient died. Accordingly, that evidence provides no support at all for PharmaStem's theory of infringement.

With respect to defendant Cryo-Cell International, Inc., PharmaStem again introduced statements from the company's website that cord blood is a source of stem cells for the child or "possibly" other family members. PharmaStem's expert witness, Dr. Hendrix, interpreted that statement to refer to adult family members and to constitute a representation that each unit of cord blood preserved by Cryo-Cell contains enough stem cells to reconstitute an adult. The statements about possible use for other family members, however, do not amount to representations that any single stored unit would be sufficient by itself to reconstitute an

adult, much less that all of the samples have that capacity.

Similarly, PharmaStem introduced evidence that defendant ViaCell, Inc., had advertised that cord blood could be stored "for potential use by a sibling, parent, first cousin or the newborn itself." While ViaCell's promotional materials stated that cord blood had been used in adult transplantation efforts, PharmaStem points to no representation by ViaCell that a single unit of its stored cord blood had ever been successfully used to effect hematopoietic reconstitution of an adult.

B

In addition to the evidence of the defendants' statements, PharmaStem also relied on evidence that each of the defendants tested their cord blood samples before cryopreserving them. Like the defendants' statements, however, that evidence also failed to establish that the preserved samples contained sufficient numbers of stem cells to effect hematopoietic reconstitution of an adult. The testing evidence showed that the defendants used various means to screen the cord blood samples before submitting them for cryopreservation. Those tests included determining whether the samples contained more than a minimum volume of blood, whether the samples were free of contamination, and whether they contained a minimum number of viable nucleated cells. Each of those testing measures was designed to increase the likelihood that the cord blood units contained viable stem cells and could be therapeutically useful. That evidence did not show, however, that the testing excluded all samples that

lacked the capacity to reconstitute an adult, because there was no showing that the defendants chose to preserve only those samples that contained sufficient stem cells for adult reconstitution, much less that their testing procedures had that effect. Nor did PharmaStem argue that the defendants' tests could be used to show that some subset of all of the preserved samples contained enough stem cells to reconstitute an adult. To the contrary, the evidence showed that the defendants saved cord blood samples when the defendants thought the samples might be of some potential therapeutic use, which would include transplantation of an infant or a young child.

C

In its brief on appeal, PharmaStem refers to two pieces of scientific evidence introduced at trial that PharmaStem contends support its claim of infringement of the '681 patent. The first is a paper published in 2001 in the New England Journal of Medicine regarding the use of umbilical cord blood in adult transplantations. That paper was cited in promotional materials of CBR and CorCell. Although the paper showed that cord blood could have restorative effects for adults, it did not disclose whether any or all of the transplantations consisted of only a single cord blood unit. The paper therefore did nothing to prove how often a single cord blood unit from a single infant is sufficient for adult reconstitution. For that reason, the 2001 paper provided no evidentiary basis from which to infer that the particular cord blood samples preserved by

any of the defendants contained a sufficient quantity of stem cells for adult reconstitution.

A second piece of scientific evidence featured by PharmaStem is a 2003 publication by the federal Food and Drug Administration reporting that an advisory committee studying cord blood transplantations had recommended that physicians be permitted to conduct adult transplantations "as long as the stem cell dose is adequate." That evidence is likewise not probative of infringement because the report makes no reference to whether a single unit of cord blood would be used in such transplantations. In fact, the transplant physician who made the presentation that led to the advisory committee's recommendation explained at trial that his recommendation against limiting transplants by age was "[b]ecause we could do cord blood transplants using two cord blood transplant [units]."

Thus, neither of the scientific exhibits cited by PharmaStem addresses whether a single cord blood unit from a single infant is sufficient to reconstitute an adult's hematopoietic system. Moreover, and significantly, neither addresses the critical question whether the particular samples preserved by the defendants contained sufficient stem cells for that purpose. Those two pieces of scientific evidence therefore do not overcome the problem with PharmaStem's evidence that the district court pointed out—that while PharmaStem may have demonstrated that the preserved cord blood units had significant therapeutic uses, and while cord blood in some amounts could be used to treat adults, the evidence was not sufficient to show that the

particular cord blood units stored by the defendants contained sufficient numbers of stem cells to reconstitute the hematopoietic system of a human adult.

D

PharmaStem's failure to establish that any of the preserved cord blood samples contained sufficient stem cells to reconstitute an adult was not merely a technical flaw in its proof. The evidence at trial showed that the great majority of cord blood transplantations between the first successful transplantation in 1988 and the time of trial had been in children. Indeed, it was not until 1995 that a cord blood transplant was even attempted in an adult. The evidence also showed that more than a single unit of cord blood was used for most cord blood transplants performed on adults; the single unit collected at an individual's birth was frequently regarded as insufficient to effect hematopoietic reconstitution of an adult.

In support of its infringement claim, PharmaStem points out that each of the defendants provided a small number of cord blood units to transplant physicians for use in transplantation procedures. The evidence shows that the four defendants had provided a total of 33 units of cord blood to transplanters by the time of trial. For the most part, however, that evidence did not distinguish between transplantations of children and transplantations of adults. To the extent that the evidence distinguished between the two, it showed that most of the supplied samples were used for transplantations of children. Moreover, with respect

to the adult transplantations, PharmaStem has not pointed to any evidence that even a single transplanted cord blood unit from one of the defendants resulted in the successful reconstitution of the hematopoietic system of an adult. Thus, the evidence regarding the transplants generally, and the defendants' experience with transplants in particular, provides no basis from which to infer that some or all of the cord blood units preserved by the defendants must have contained a sufficient number of stem cells for adult reconstitution. For that reason, the district court was correct to hold that the evidence was insufficient to support the jury's verdict of infringement of the '681 patent.

Contrary to PharmaStem's contention, the district court's ruling did not convert a determination as to damages into a ruling on liability. Because of the manner in which PharmaStem sought to prove infringement, it committed itself to a course that had "all-or-nothing" consequences. The district court was correct to conclude that, having chosen not to try to prove that particular cord blood samples or categories of samples contained sufficient stem cells to effect hematopoietic reconstitution of an adult, PharmaStem took the risk that the court would conclude that it had failed to prove that any of the defendants' cryopreserved samples infringed. The district court's narrow disposition of the JMOL issue simply held PharmaStem to the consequences of the strategy it adopted at trial.

E

In reaching this conclusion, we reject PharmaStem's contention that the district court

abused its discretion when it determined, following the trial, that the infringement opinion of PharmaStem's expert witness Dr. Hendrix should have been struck. The district court found her testimony unhelpful to the jury, and not an appropriate subject for expert evidence, because it consisted almost entirely of her quoting from the promotional information and other materials in which the defendants described their business operations for potential customers and investors, and drawing inferences from those materials. The district court did not abuse its discretion in concluding that the jury was fully capable of understanding those materials without expert assistance and that Dr. Hendrix's testimony should have been excluded. See General Electric Co. v. Joiner, 522 U.S. 136, 141 (1997) (abuse of discretion standard applies to district court's decision to exclude expert testimony).

Dr. Hendrix concluded from those materials that the defendants had in effect admitted that all of the cord blood samples that the defendants preserved contained a sufficient quantity of stem cells to reconstitute an adult. In particular, Dr. Hendrix interpreted the defendants' statements about their processes for preserving cord blood samples to mean that each of them tested the samples "to determine if there is a sufficient amount of cells for reconstitution for an adult. And then after that time, they cryopreserve it for storage." She admitted that she did not examine the data obtained by the defendants from their testing of the samples; that she did not know how many, if any, successful adult transplantations had been done with cord blood

samples preserved by any of the defendants; and that she did not know whether, when the defendants tested the samples, they determined whether the samples were "sufficient for an adult or sufficient for a child or sufficient for any purpose." In sum, Dr. Hendrix admitted that a particular company's decision to store a particular sample did not necessarily mean the sample was sufficient to reconstitute an adult. Nonetheless, she maintained that "[i]f the cord bloods are being stored, and the companies promise that—I mean they state in their websites that there are sufficient cells that they make available for transplantation, pediatric, sibling, older and adults, then I believe that there is the potential in all of those samples that are stored in frozen sanctuary to provide that service."

There are two problems with Dr. Hendrix's testimony, as the district court pointed out. First, because her testimony was almost entirely based on an interpretation of the defendants' marketing materials and materials directed to investors, any expertise on Dr. Hendrix's part as a cell biologist was of no apparent help to the jury. Whether or not the materials constituted admissions by the defendants that some or all of the preserved samples contained enough stem cells to reconstitute an adult was not a matter as to which Dr. Hendrix's expertise was of any apparent use. See Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 592 (1993) (admission of expert testimony "is premised on an assumption that the expert's opinion will have a reliable basis in the knowledge and experience of his discipline"). Second, not only was her expertise not necessary or useful to interpret the defendants' materials, but her

interpretation was not a reasonable one. Nowhere did the defendants represent that any of the preserved cord blood samples (much less all of them) contained a sufficient number of stem cells to reconstitute an adult. The representations that the cord blood was of potential use not only for infants and children but also for adults falls significantly short of a representation that the individual cryopreserved cord blood samples each contained enough stem cells to reconstitute an adult.

To be sure, Dr. Hendrix stated in conclusory terms that she relied for her opinion not only on the defendants' materials, but also on scientific literature, testimony of experts, and the depositions of representatives of the defendants. She made clear, however, that her opinion was based principally on the assertions by the defendants that the preserved cord blood had potential uses for adults as well as for children. Moreover, Dr. Hendrix did not explain how her reliance on any of the other sources of information supported her inference about whether the defendants' preserved samples contained an infringing quantity of stem cells.

In short, we agree with the trial court that the defendants' materials did not constitute sufficient proof of infringement of the '681 patent and that those materials did not become proof of infringement when Dr. Hendrix read those materials back to the jury from the witness stand. There was therefore nothing in Dr. Hendrix's testimony that sufficed to remedy the insufficiency that the district court pointed out in PharmaStem's other evidence of infringement of the '681 patent.

IV

With respect to infringement of the '553 patent, the issue presented to us is again a narrow one. There is no dispute that in the 33 instances in which the defendants' cord blood samples were used in transplant procedures, samples of cord blood containing stem cells were collected, cryopreserved, thawed, and introduced into the patient's body. In no case, however, were all those steps performed by the same party. Instead, the defendants were typically responsible for collecting and cryopreserving the cord blood samples, while transplant physicians unrelated to the defendants thawed the cord blood and used it for transplanting.

In light of the fact that the defendants did not perform all the steps of the patented method, PharmaStem based its claim of infringement of the '553 patent on the theory of contributory infringement. The district court instructed the jury on contributory infringement and gave the jury special verdict questions that directed the jury's inquiry to the requirements of that theory.

The court instructed the jury that in order to prove contributory infringement, PharmaStem was required to prove, inter alia, (1) that the defendants "sold or offered to sell cryopreserved cord blood to a transplanter" and (2) that the cryopreserved cord blood that was "sold or offered for sale by the defendant was used by a single entity, or alternatively, by a group of entities that are acting in concert or working together to complete the process of infringement." The pertinent special verdict questions corresponding to those instructions

required the jury to find that "the defendants and the transplant physicians are acting in concert or working together to complete the process of infringement" of the asserted claims of the '553 patent (special verdict question 4) and that the defendants "contributorily infringed the '553 patent by selling or offering to sell cryopreserved cord blood that was actually used by a third party in the direct infringement" of any of the asserted claims (special verdict question 5).

PharmaStem's theory of contributory infringement was based on the contributory infringement section of the Patent Act, 35 U.S.C. § 271(c), which provides: "Whoever offers to sell or sells . . . a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent" shall be liable as a contributory infringer. The jury found in PharmaStem's favor on each of the special verdict questions pertaining to contributory infringement and accordingly returned a verdict of liability against all of the defendants on the '553 patent.

The issue on appeal is whether there was substantial evidence to support the jury's finding, in response to special verdict question 5, that each of the defendants "contributorily infringed the '553 patent by selling or offering to sell cryopreserved cord blood that was actually used by a third party in . . . direct infringement" of that patent. The district

court ruled that the evidence was sufficient to show that the defendants sold a service to families of newborn infants (collection, processing, and cryopreservation of the newborn's umbilical cord blood), but not to show that they sold the cord blood units themselves, which belonged to the families throughout, and certainly not to show that the defendants sold the cord blood units to the transplanters.

The district court construed the contributory infringement statute to require a sale or an offer of sale of a product; the statute is not satisfied, the court ruled, by the provision of a service for compensation. Because liability under section 271(c) "is clearly dependent upon the accused infringer's selling or offering to sell a component of the patented process, here cord blood units," the court held that the jury's verdict on contributory infringement could not stand, and it therefore granted the defendants' JMOL motions with respect to the '553 patent.

In challenging the district court's ruling, PharmaStem first argues that the jury could properly characterize as a "sale" the transaction in which the defendants obtained unprocessed umbilical cord blood, converted it into a therapeutically useful, cryopreserved cord blood product, and later provided it to transplant physicians at the behest of the client family. While cord blood is certainly a product, the transaction between the defendants and their clients is plainly not the sale of "a material or apparatus for use in practicing a patented process," as is required by section 271(c) with respect to method patents. The

evidence at trial showed that the cord blood remained the property of the families throughout the period in which the defendants stored it. The defendants were never owners of the blood, but instead were merely bailees; they were not free to dispose of the blood as they chose, but were contractually obligated to preserve it pending the families' need for it at some point in the future. On those occasions when the cord blood was needed, the defendants provided the blood to transplanters in satisfaction of their contractual obligation to ship the families' cord blood samples to a transplanter upon direction. Neither that transaction nor any earlier transaction between the families and the defendants constituted a "sale" of the cord blood. See Sturm v. Boker, 150 U.S. 312, 329–30 (1893) ("The recognized distinction between bailment and sale is that, when the identical article is to be returned in the same or in some altered form, the contract is one of bailment, and the title to the property is not changed. On the other hand, when there is no obligation to return the specific article, and the receiver is at liberty to return another thing of value, he becomes a debtor to make the return, and the title to the property is changed."). Rather, as the trial court held, the transaction between the families and the defendants constituted the provision of a service for a fee.

In the alternative, PharmaStem argues that even if the district court was correct to characterize the defendants' activities as providing a service rather than selling a product, the court still should have upheld the jury's verdict of contributory infringement. In this regard, PharmaStem argues

that section 271(c) is not limited to the sale of a product, but extends to the sale of a service.

PharmaStem's argument is contrary to both the language and the legislative history of section 271(c). The statute provides, in pertinent part, that a contributory infringer is one who "offers to sell or sells within the United States a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process." Although that language describes in various different ways the items that may be sold for purposes of creating liability for contributory infringement, all of the descriptions refer to the sale of a product of some sort; none of them refer to the provision of a service. Under the plain language of the statute, a person who provides a service that assists another in committing patent infringement may be subject to liability under section 271(b) for active inducement of infringement, but not under section 271(c) for contributory infringement.

The legislative background of section 271(c) makes clear that the district court was correct to construe that statute as confined to its plain terms. Prior to the 1952 Patent Act, no statute defined contributory infringement. Instead, as a result of court decisions, infringement was divided into two categories: "direct infringement," which was the unauthorized making, using, or selling of the patented invention, and "contributory infringement," which was "any other activity where, although not technically making, using, or selling, the defendant displayed sufficient culpability to be held liable as an infringer." Hewlett-Packard Co. v. Bausch & Lomb

Inc., 909 F.2d 1464, 1469 (Fed. Cir. 1990). The 1952 Act did not make a substantive change in the law of contributory infringement, but it divided the judicially created category of contributory infringement into two statutory subsections, section 271(b) (inducement of infringement) and section 271(c) (contributory infringement). The most common type of pre-1952 contributory infringement cases were those in which "a seller would sell a component that was not covered by the claims of a patent but which had no other use except the claimed product or process." Id. That form of contributory infringement was codified in section 271(c). Id.

The Senate Report on the 1952 Act confirms that section 271(c) was intended to deal with a particular subset of what had previously been considered contributory infringement, consisting of cases in which a party sells a particular component that is known to be intended for an infringing use and is useful only for infringement. The Senate Report states that section 271(b) recites "in broad terms that one who aids and abets an infringement is likewise an infringer" whereas section 271(c) deals specifically with the most common form of contributory infringement and "is much more restricted than many proponents of contributory infringement believe should be the case." S. Rep. No. 89-1959, at 8, 28 (1952) (characterizing section 271(c) as applying to "one who sells a component part of a patented invention or material or apparatus for use therein"), reprinted in 1952 U.S.C.C.A.N. 2394, 2402, 2421; see also Jones v. Radio Corp. of Am., 131 F. Supp. 83, 83 (S.D.N.Y. 1955) (in light of legislative

history of 1952 Act, section 271(c) does not apply if the defendant did not sell a component of the patented combination).

In summary, the district court correctly concluded that the defendants did not sell a product and that what they provided to customers was a service for compensation. The evidence showed that the cord blood the defendants collected and preserved was never their property; instead, it remained the property of the families who engaged their services. The defendants were never the owners of the blood and thus never "sold" the blood to the families when it was needed. The district court therefore properly held that the defendants could not be found liable for contributory infringement under section 271(c).[1]

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[1] The parties and the district court discussed the issue of joint infringement in the context of determining whether there was infringing conduct sufficient to serve as a predicate for a finding of contributory infringement. PharmaStem did not argue before the district court, and does not argue here, that liability could be premised on a theory of "joint" or "divided" infringement, even in the absence of a finding of contributory infringement under 35 U.S.C. § 271(c). Under that theory, two related parties are both deemed liable for direct infringement of a method patent when each performs some steps of the claimed method. The viability and scope of that theory of liability is a subject of considerable debate; it has been addressed in a number of district court cases, adverted to in a few of this court's cases, and discussed at some length by commentators. See On Demand Mach. Corp. v. Ingram Indus., Inc., 442 F.3d 1331, 1334 (Fed. Cir. 2006); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1311 (Fed. Cir. 2005); Kristin E. Gerdelman, Subsequent Performance of Process Steps by Different Entities: Time to Close Another Loophole in U.S. Patent Law, 53 Emory L.J. 1987 (2004); Mark

There is another reason why the jury's verdict in this case cannot stand. The court instructed the jury, without objection from PharmaStem, that it was necessary for the sale in question to be made "to a transplanter." Yet even if a sale of a service were deemed sufficient to constitute a "sale" for purposes of section 271(c), there was no evidence that any of the defendants made a sale of either products or services to the transplanters. To the contrary, the evidence showed that the service the defendants provided was a service to the donor families, for which the families paid a fee, and that there was no sale of any sort by the defendants to the transplanters or any fee paid by the transplanters to the defendants. The defendants simply transferred the cord blood units to designated transplanters upon direction from the families. Such a transaction does not constitute a "sale" to a transplanter under any definition of the term "sale." Accordingly, the district court properly concluded that the jury's verdict was legally insufficient to establish infringement under the law of the case as given by

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A. Lemley et al., Divided Infringement Claims, 33 AIPLA Q.J. 255 (2005); Sriranga Veeraraghavan, Joint Infringement of Patent Claims: Advice for Patentees, 23 Santa Clara Computer & High Tech L.J. 211 (2006). That issue is squarely presented in a case now pending before this court, BMC Resources, Inc. v. Paymentech, L.P., No. 2006-1503. In this case, PharmaStem's theory of liability was that the defendants were liable under section 271(c) for contributory infringement, not under section 271(a) for direct infringement, and PharmaStem has continued to press that theory on appeal. We therefore are not presented with the question whether the defendants could have been held liable under section 271(a) under a theory of joint direct infringement through their activities in conjunction with the transplanters.

the court to the jury and accepted by the parties. We therefore uphold the portion of the court's judgment granting the defendants' JMOL motions with respect to the '553 patent.

V

The jury returned verdicts in favor of PharmaStem on the defendants' counterclaims challenging the validity of the two patents in suit. In its opinion on the defendants' JMOL motions, the district court held that the jury's verdicts on the validity issues were supported by substantial evidence. In their cross-appeal, the defendants contest the portions of the trial court's judgment rejecting their challenges to the patents on grounds of anticipation, obviousness, and (in the case of the '681 patent) indefiniteness. Each of those issues presents a close question. Because we hold that the district court should have granted the defendants' motion for JMOL on the issue of obviousness, it is not necessary for us to address the defendants' arguments with respect to the issues of indefiniteness and anticipation.

A

Obviousness is a legal conclusion that we review de novo. The statutory standard requires us to decide whether the subject matter of the claimed invention "would have been obvious at the time the invention was made to a person of ordinary skill in the art to which [the subject matter of the invention] pertains." 35 U.S.C. § 103(a); Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006); DyStar Textilfarben GmbH & Co.

Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006). Underpinning that legal issue are factual questions relating to the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations, such as commercial success, long-felt need, and the failure of others. See Eli Lilly, 471 F.3d at 1377; DyStar, 464 F.3d at 1360; Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1164 (Fed. Cir. 2006). Under Third Circuit law, which in this case dictates the standard for reviewing the denial of the motion for JMOL, we review the district court's action "de novo by reapplying the JMOL standard" applied by the district court. Seachange Int'l, Inc. v. C-COR Inc., 413 F.3d 1361, 1368 (Fed. Cir. 2005). Thus, in reviewing the denial of the JMOL motion on the issue of obviousness, we examine the evidence in the light most favorable to the verdict and determine whether a reasonable jury could have found all the facts necessary to support the verdict of nonobviousness, i.e., whether substantial evidence supports the verdict. See Caver v. City of Trenton, 420 F.3d 243, 262 (3d Cir. 2005); Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1546 (Fed. Cir. 1983).

B

The defendants contend that the two patents in suit are invalid for obviousness based on a combination of several prior art references. In such a case, the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry

out the claimed process, and would have had a reasonable expectation of success in doing so. See Medichem, 437 F.3d at 1164; Noelle v. Lederman, 355 F.3d 1343, 1351–52 (Fed. Cir. 2004); Brown & Williamson Tobacco Co. v. Philip Morris, Inc., 229 F.3d 1120, 1121 (Fed. Cir. 2000); see also KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007) (a combination of elements "must do more than yield a predictable result"; combining elements that work together "in an unexpected and fruitful manner" would not have been obvious).

In view of the prior art references, the first part of that test is plainly satisfied here. The idea of using cryopreserved cord blood to effect hematopoietic reconstitution was not new at the time the inventors filed the applications that matured into the '681 and '553 patents. Two of the prior art references—articles by Ende and Knudtzon—suggest using cord blood for that purpose. Two others—an article by Koike and a doctoral dissertation by Vidal—suggest cryopreservation and storage of the cord blood until needed. Accordingly, this is not a case in which there is any serious question whether there was a suggestion or motivation to devise the patented composition or process.

The more difficult question is whether the prior art would have given rise to a reasonable expectation of success in creating the process claimed in the '553 patent and the composition claimed in the '681 patent. In addressing that question, the parties focus on whether the inventors had a reasonable expectation that cord blood could be successfully used in transplants for hematopoietic reconstitution.

On the question whether the inventors had a reasonable expectation of success, the district court relied principally on testimony by PharmaStem's expert, Dr. Irwin Bernstein. In testimony cited by the court, Dr. Bernstein explained that there were problems with transplant tissues that had been used previously, including bone marrow and adult blood; that those working in the transplant field did not believe blood would be suitable as a transplant tissue; and that researchers in his group were surprised at the successful result of the first transplant of cord blood into a human. That evidence, according to the court, justified the jury in finding that persons of skill in the field of hematopoietic reconstitution "would not have expected cord blood to be a successful transplant tissue." In light of that evidence and the evidence of secondary considerations such as long-felt need and commercial success, and in light of the PTO's issuance of the patents over several of the prior art references that were in issue at trial, the court concluded that "there is no basis to overturn the jury's verdict that the Patents-In-Suit are not obvious."

The defendants argue that the prior art suggested using cryopreserved cord blood for hematopoietic reconstitution and showed that persons of skill in the field would have had a reasonable expectation that the use of cord blood in transplants would be successful. For that reason, according to the defendants, the asserted claims were obvious as a matter of law.

Like the district court, PharmaStem relies principally on Dr. Bernstein's testimony to support its argument that the asserted claims of the '681 and '553 patents were not invalid for obviousness. Citing his testimony, PharmaStem argues that those skilled in the art at the time of the inventions "did not even yet know of the presence of stem cells in cord blood." PharmaStem argues that Dr. Bernstein's assertion that it was not known that cord blood contained stem cells, combined with his testimony regarding problems with transplant tissues used prior to the '681 and '553 patents, shows that those in the field of hematopoietic reconstitution "would not have expected cord blood to be a successful transplant tissue."

The cornerstone of Dr. Bernstein's testimony at trial was that none of the prior art showed that cord blood contains stem cells. According to Dr. Bernstein, the presence of stem cells in cord blood was not conclusively established before the mouse studies described in the joint specification and the 1988 human cord blood transplant referred to in the specification of the '553 patent.

The problem with Dr. Bernstein's testimony about the prior art references is that it cannot be reconciled with statements made by the inventors in the joint specification and with the prior art references themselves. Dr. Bernstein distinguished each of the prior art references on the ground that none of them disclosed the presence of stem cells in cord blood. Even though some of the references referred to stem cells as being present in cord blood, Dr. Bernstein took the position that those statements

in the prior art references reflected flawed nomenclature and that the most the data underlying the prior art references showed was that cord blood contained progenitor cells. Progenitor cells are the cells that generate several different types of cells that make up the blood and immune system but are less primitive than hematopoietic stem cells. According to Dr. Bernstein, it was not proved that stem cells, as opposed to the less primitive progenitor cells, are present in cord blood until the patentees performed the mouse experiments reported in the joint specification. Those experiments showed that relatively small amounts of fetal blood were sufficient to effect hematopoietic reconstitution in lethally irradiated mice. Dr. Bernstein added that in light of the poor results obtained with transplantations of adult blood "it had to take a leap of thinking that cord blood was different."

The joint specification, however, tells a different story. There, the inventors acknowledged that it was previously known that the properties of cord blood are quite different from those of adult blood and that hematopoietic stem cells had been found in cord blood in much greater concentrations than in adult blood. Citing a number of references, the inventors stated the following:

> A human hematopoietic colony-forming cell with the ability to generate progenitors for secondary colonies has been identified in human umbilical cord blood. In addition, hematopoietic stem cells have been demonstrated in human umbilical cord blood, by colony

> formation, to occur at a much higher level than that found in the adult. The presence of circulating hematopoietic progenitor cells in human fetal blood has also been shown. Human fetal and neonatal blood has been reported to contain megakaryocyte and burst erythroblast progenitors with increased numbers of erythroid progenitors in human cord blood or fetal liver relative to adult blood.

'681 patent, col. 4, ll. 15-34 (citations omitted); '553 patent, col. 4, ll. 21-42 (citations omitted).

That excerpt from the specification cannot be squared with Dr. Bernstein's characterization of the prior art. Contrary to Dr. Bernstein's contention that the prior art did not disclose the presence of stem cells in cord blood, the inventors cited several prior art references and stated flatly that "hematopoietic stem cells have been demonstrated in human umbilical cord blood." Moreover, the inventors noted that the prior art references showed that the concentration of stem cells in cord blood was "at a much higher level than in the adult." Nor can those statements in the specification be dismissed as reflecting a careless use of the term "hematopoietic stem cell," i.e., the use of that term when the inventors meant to refer to progenitor cells. That is made clear by context, as the sentence that immediately follows the reference to "hematopoietic stem cells" states that "the presence of hematopoietic progenitor cells in human fetal blood has also been shown."

Accordingly, PharmaStem's argument that stem cells had not been proved to exist in cord blood prior to the experiments described in the patents is contrary to the representation in the specification that the prior art disclosed stem cells in cord blood. Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness. See Constant v. Advanced Micro Devices, Inc., 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in the patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness."); Sjolund v. Musland, 847 F.2d 1573, 1577-79 (Fed. Cir. 1988) (patent specification admitted that certain matter was prior art, and thus "the jury was not free to disregard [that matter]" and "must have accepted [it] as prior art, as a matter of law"); In re Fout, 675 F.2d 297, 300 (CCPA 1982); In re Nomiya, 509 F.2d 566, 571 (CCPA 1975).

Nor is there any unfairness in holding the inventors to the consequences of their admissions, as their characterization of the prior art as showing the presence of stem cells in cord blood is hardly unreasonable. At trial, the defendants' expert acknowledged that, prior to the time of the first successful cord blood transplant, stem cells could not be conclusively proved to be present in cord blood. He explained, however, that in light of the discovery of substantial numbers of progenitor cells in cord blood—roughly equivalent to the number of such cells in bone marrow—it was appropriate for the authors of the prior art references to infer the

presence of stem cells in cord blood, even though positive proof of their presence was not available.

The prior art references provide strong support for that interpretation. Mouse studies reported by Barnes in a 1964 article showed that the blood of fetal and neonatal mice contained a much greater concentration of colony-forming units (i.e., progenitor cells) than adult blood. Barnes identified the colonies in question as containing stem cells. A 1974 article by Knudtzon similarly noted that an "increased concentration of hemopoietic stem cells has been found in the blood of mouse embryos when compared to the concentration after birth." Knudtzon also conducted tests on human umbilical cord blood, determining that the concentration of in vitro colony-forming cells in cord blood is likewise much greater than in human adult blood and that the concentration is comparable to the concentration in bone marrow tissue. Knudtzon concluded that "the finding of an increased concentration of colony-forming cells in human cord blood comparable in number with human bone marrow cultures indicates that cord blood might be used as a source of hemopoietic stem cells for the restoration of bone marrow function in humans." Two years later, a case study by Ende reported a transfusion of 45 milliliters of human cord blood into a human patient, which resulted in a temporary hematopoietic graft that lasted for five weeks. Ende cited other research indicating that a similar or even larger amount of bone marrow would be needed to achieve a successful permanent graft.

A 1978 article by Prindull noted that animal experiments showed that fetal blood contains more than 100 times as many stem cells as are present in adult blood and suggested that because the fetal hematopoietic system is in a state of physiologic proliferation, human cord blood could constitute a source of hematopoietic stem cells. An article by Koike, in 1982, described the results of freezing and thawing cells derived from bone marrow and cord blood. It showed that even immature progenitor cells can survive cryopreservation and concluded that because cord blood contains "many pluripotent and nearby progenitor cells comparable to marrow cells," cord blood or other fetal tissue could be a useful source of hematopoietic progenitor cells for transplantation. In 1985, a doctoral dissertation by Vidal concluded, based on various studies, that "cord blood contains sufficient hematopoietic stem cells to effect a transplant," that "cord blood can be used for this purpose," and that "cryopreserved cord blood banks might exist."

That collection of prior art shows (1) that bone marrow transplants can result in hematopoietic reconstitution; (2) that cord blood, like bone marrow but unlike adult blood, contains large numbers of progenitor cells; and (3) that the high concentration of primitive progenitor cells in cord blood suggests that in humans, as in mice, the cells responsible for hematopoiesis migrate at about the time of birth from fetal organs to the bone marrow. Under those circumstances, it was reasonable for the inventors of the patent, like the authors of the prior art references, to infer the presence of high concentrations of stem cells in cord blood, even

though the prior art studies did not offer conclusive proof of their presence.

C

Given that the jury was legally required to find that that those of skill in the art would believe that cord blood contained hematopoietic stem cells, the question before us is whether a reasonable jury could nonetheless have found the invention nonobvious. We conclude a reasonable jury could not have done so. While the inventors may have proved conclusively what was strongly suspected before—that umbilical cord blood is capable of hematopoietic reconstitution—and while their work may have significantly advanced the state of the science of hematopoietic transplantations by eliminating any doubt as to the presence of stem cells in cord blood, the mouse experiments and the conclusions drawn from them were not inventive in nature. Instead, the inventors merely used routine research methods to prove what was already believed to be the case. Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention. See KSR, 127 S. Ct. at 1732 ("Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress . . . ."); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367-69 (Fed. Cir. 2007) (simply because the formation and properties of a new compound must be verified through testing does not mean that the compound satisfies the test for patentability "since the expectation of success need only be reasonable, not absolute"); In re Merck & Co., 800 F.2d 1091, 1097

(Fed. Cir. 1986) ("Obviousness does not require absolute predictability."). Good science and useful contributions do not necessarily result in patentability.

This court's decision in In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988), provides useful guidance for determining whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious. The court noted that obviousness "does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice." 853 F.2d at 903. On the other hand, the court explained, an invention would not be invalid for obviousness if the inventor would have been motivated "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Id. Likewise, an invention would not be deemed obvious if all that was suggested "was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." Id.; see also Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1166-67 (Fed. Cir. 2006).

This case is not one in which "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible

choices is likely to be successful," nor is it one in which the prior art "gave only general guidance as to the particular form of the invention or how to achieve it." O'Farrell, 853 F.2d at 903. The prior art suggested cryopreserving cord blood from a single infant and transplanting that blood into a patient to achieve hematopoietic reconstitution. PharmaStem does not suggest, and Dr. Bernstein's testimony did not reveal, that there was an array of possible choices as to how to achieve that objective or that there were problems to be solved in implementing the prior art suggestion that were not adumbrated in the prior art. To the contrary, the joint specification indicates that each step of the cryopreservation and transplantation procedure had been spelled out in the prior art. PharmaStem does not claim that there was anything novel about the method by which it proposed to collect, cryopreserve, and transplant the cord blood. Instead, in responding to the defendants' obviousness challenge, PharmaStem focuses entirely on the purported novelty of its proof that stem cells are present in fetal blood, a demonstration that Dr. Bernstein testified was necessary to give transplant physicians sufficient confidence in the use of cord blood for hematopoietic reconstitution to try the procedure on humans. As we have explained, however, providing proof sufficient to justify conducting in vivo procedures on humans, while useful, is not a test of patentability. The evidence at trial demonstrated that the patentees did not invent a new procedure or a new composition; instead, they simply provided experimental proof that the cord blood could be used to effect hematopoietic reconstitution of mice and, by extrapolation, could be expected to work in humans as well.

D

In addition to its reliance on Dr. Bernstein's testimony about the prior art references, PharmaStem invokes various secondary considerations that it contends support the jury's verdict on obviousness. In particular, PharmaStem points to evidence that the inventors were widely recognized as pioneers in the use of cord blood for hematopoietic reconstitution, including statements by the defendants and their representatives. Defendant ViaCord's business plan praised the inventors as "trailblazers," and a founder of defendant Cryo-Cell wrote to the inventors' company and stated: "[N]o one will ever dispute that you, as the pioneers in the medical technology . . . will be the frontrunners in the field of utilizing the blood from the umbilical cord for restoring hematopoietic [sic] through marrow transplants." Even the defendants' expert had previously referred to the inventors as the first to suggest the use of human umbilical cord blood as a source of transplantable hematopoietic stem cells, although he disclaimed those statements at trial on the ground that he had subsequently determined that it was incorrect to give the inventors credit for conceiving the invention. The problem with that evidence is that there was no indication that the praise for the inventors' work was based on any inventive contribution they made, as opposed to their proof, through laboratory work, that fetal blood contains large numbers of stem cells. As noted, the former is a basis for patentability; the latter is not.

PharmaStem also points to Dr. Bernstein's testimony that researchers in his group in Seattle

were "surprised" at the successful human cord blood transplantation in 1988. There are two problems with that evidence. First, there was no indication that either Dr. Bernstein or members of his research group were previously aware of the prior art references that laid the groundwork for the inventors' experiments. Dr. Bernstein stated that his surprise at the successful use of cord blood was based on the poor results obtained with transplants of adult blood; he did not state that the success of the human transplant would have been surprising to one familiar with the prior art references introduced at trial, including those references that featured the important differences between adult blood and cord blood as potential transplant tissues.

Second, Dr. Bernstein tied the "surprise" of his research group to the success of the 1988 human cord blood transplant, not to the results reported in the patents. Although the transplant was based on work done by the inventors, it took place long after the filing of the application for the '681 patent and shortly before the filing of the application for the '553 patent. As a result, the specification of the '681 patent does not refer to the 1988 transplant at all, and the specification of the '553 patent does not contain any account of the results of that transplant. At the time of the application for the '553 patent, all that was known and disclosed about the 1988 transplant was that it had been attempted.

Moreover, although it is true, as PharmaStem argued, that physicians began performing human transplants only after the inventors conducted their mouse experiments, the evidence at trial showed

that physicians were reluctant to try a new procedure such as a cord blood transplant on humans without a very strong scientific basis for concluding that it was likely to work. The prior art already indicated that cord blood was likely to be a valuable source of hematopoietic stem cells; the mouse studies merely provided supporting evidence for that conclusion, evidence that the transplant physicians regarded as sufficient to justify trying the procedure on a human child.

E

Finally, PharmaStem argues that the jury's verdict is supported by the decision of the Patent and Trademark Office ("PTO") to issue the '681 and '553 patents, and to confirm the '681 patent following reexamination, over some of the same references that the defendants cited at trial. When the party asserting invalidity relies on references that were considered during examination or reexamination, that party "bears the added burden of overcoming the deference that is due to a qualified government agency presumed to have done its job." Polaroid Corp. v. Eastman Kodak Co., 789 F.2d 1556, 1560 (Fed. Cir. 1986); see also AI-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999).

The examiner who issued the reexamination certificate for the '681 patent summarized her analysis of the prior art by stating that none of the cited references "addresses the presence of hematopoietic stem cells in umbilical cord or placental blood, that these cells may successfully be cryopreserved, or that, as a collection from a single human at birth, these cells may comprise an amount

that is sufficient to effect hematopoietic reconstitution of a human adult." That explanation is flawed for three reasons. First, as we have explained, the prior art references and the admissions in the specification address the presence of hematopoietic stem cells in cord blood, even though the references may not conclusively prove their presence. Second, Koike established that cord blood could be cryopreserved without substantial losses in the population of progenitor cells; the inventors contributed nothing more with respect to cryopreservation, as their mouse experiments were not performed with cryopreserved blood. Third, while the joint specification states that the amount of cord blood obtained at the time of birth would often be sufficient to transplant an adult, the inventors reached that conclusion simply by comparing the known properties of bone marrow against the results of routine testing of their own cord blood samples.

The specification explains that, because of the inability to determine the number of stem cells present in a particular composition, researchers and transplanters use surrogate assays from which they can infer that stem cells are present and in roughly what numbers. One of the surrogate assays that the joint specification describes in detail and that was the subject of testimony at trial is the assay for CFU-GM (colony-forming units for granulyte and macrophage cells), i.e., progenitor cells that produce the more specialized granulyte and macrophage cells. The inventors compared the results of conventional CFU-GM assays of cord blood samples with published reports of the number of CFU-GM in bone marrow samples sufficient for successful hema-

topoietic reconstitution. '681 patent, col. 50, line 64, to col. 51, line 15; '553 patent, col. 51, ll. 44-68. Thus, the inventors reported that prior art studies showed that in cases involving autologous bone marrow transplants, "rapid repopulation of hematopoiesis in patients with acute leukemia was associated with as few as 0.25 million progenitor cells [CFU-GM]." '681 patent, col. 13, ll. 49-54. The inventors' assays of cord blood samples, confirmed by prior art studies, showed that 50 milliliters of cord blood would contain up to more than 0.5 million CFU-GM. Id., col. 13, ll. 55-63. Thus, the inventors' conclusion that a single unit of cord blood can result in hematopoietic reconstitution of an adult was simply the result of a comparison between the well-known properties of bone marrow and their own conventional assays of a number of samples of cord blood.

In sum, while the issue of obviousness in this case presents us with a difficult question in light of the standards of proof and review that are applied to an appellate challenge to a jury verdict of nonobviousness, we are persuaded that there was clear and convincing evidence that the asserted claims of the '681 and '553 patents would have been obvious and that it was unreasonable for the jury to reach the opposite conclusion. We therefore reverse the denial of JMOL on that issue and remand to the district court for entry of judgment in the defendants' favor.

VI

This was a closely contested case both at trial and on appeal, and the JMOL motions presented the

district court with an unusually difficult set of challenges. We are satisfied that the district court correctly resolved each of the issues that the parties have raised and we have addressed on appeal, with the sole exception of the cross-appeal on the issue of obviousness. We therefore affirm the judgment of the district court with respect to the appeal but reverse the judgment on the cross-appeal with respect to the issue of obviousness. As to that issue, we reverse and remand to the district court for entry of judgment in the defendants' favor.

Each party shall bear its own costs for this appeal and cross-appeal.

AFFIRMED IN PART, REVERSED IN PART, and REMANDED.

United States Court of Appeals for the Federal Circuit

05-1490, -1551

PHARMASTEM THERAPEUTICS, INC.,
Plaintiff-Appellant,

v.

VIACELL, INC.,
Defendant-Cross Appellant,

and

CRYO-CELL INTERNATIONAL, INC., CORCELL, INC.,
Defendants-Cross Appellants,

and

CBR SYSTEMS, INC.
(formerly known as Cord Blood Registry, Inc.),
Defendant-Cross Appellant,

v.

BIRTHCELLS TECHNOLOGY, INC. and BIO-CELL, INC.,
Defendants.

NEWMAN, Circuit Judge, dissenting.

I respectfully dissent. After a three week trial the jury sustained the validity of these patents, the

district court in a thorough opinion upheld the verdicts of validity, and validity was confirmed in three reexaminations by the Patent and Trademark Office. Today my colleagues on this panel hold that the inventions in the '681 patent and its continuation-in-part the '553 patent are obvious to them, and not infringed.

The undisputed evidence at trial was that these long-sought life-saving inventions were achieved amid general scientific skepticism, despite the extensive research that was being conducted by many scientists in this field, as set forth in the patents in suit. The discoveries of these inventors were met with universal acclaim and widespread utilization, including the founding of many commercial enterprises, all of which are reported to have licensed the patents except for these defendants. Unimpressed by these considerations, my colleagues on this panel now reconstruct these inventions by selection and inference, with perfect hindsight of the discoveries. The evidence at trial was that this achievement eluded persons working in the field, despite speculation concerning its potential and recognition of its value if it could actually be achieved; despite the powerful interest in such a life-saving advance. Instead, my colleagues simply reweigh selectively extracted evidence, ignore the actual peer response and acclaim at the time these inventions were made, and decide that this long-sought advance would have been obvious to this court.

Inventors Edward A. Boyse, Hal E. Broxmeyer, and Gordon W. Douglas made possible a

new industry with PharmaStem's predecessor Biocyte, Inc., founded by the inventors. The record contains many publications reporting the work of these inventors, and the evidence was undisputed that they were the first to achieve the transplantation of umbilical cord stem cells for reconstitution of the human hematopoietic system. Although my colleagues manage to reconstruct this extensive scientific effort as simple routine that is obvious to judges, the processes of discovery in complex science make it particularly necessary to view the achievement in the context of the knowledge at the time the invention was made, and to judge it as it was judged by scientific peers at that time, with the assistance of the hard fact of commercial success in a field in which the need was great and success had long been eluded. See Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966) ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.") (quoted in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007)).

The panel majority scours the prior art for clues that could fit the eventual achievement, and then rules that the achievement was obvious, no matter that it eluded the others whose work is now compiled by this court so as to invalidate these patents. The "prior art" selected by my colleagues spans many years of scientific interest and effort, yet the ultimate discovery of the presence of stem cells along with or instead of progenitor cells, the

successful preservation of these cells, the extensive experimentation with transplantation into animal models and ultimately into humans, and the successful hematopoietic reconstitution of blood that has been destroyed by disease or radiation, was not achieved in the prior art. The judicial determination of "obviousness" should be made in the context of the state of knowledge at the time these inventions were made. Nor should the courts lose sight of the powerful policy that underlies the patent law, whereby recognition and protection of technological and scientific advance is legally established in order to serve the public interest in having the benefit of such advance through economic enterprise.

My colleagues ignore not only the scientific experts who testified at the trial, but also the PTO examiners who conducted the three reexaminations. In Dickinson v. Zurko, 527 U.S. 150 (1999) this court was reminded of its obligation to give appropriate deference to agency expertise, including that of the PTO. The references that are analyzed by the panel majority, in its sua sponte finding of obviousness, were before the PTO for examination and multiple reexaminations. My colleagues do not explain where the PTO went wrong; instead, they rearrange the past, criticize the acclaim heaped on these inventors, and propose that if the people in this field knew what this court knows, they would not have been so impressed.

To the contrary: the acclaim sounded by even these defendants is a powerful testament to how this invention was viewed. From my colleagues' invalidation of these patents on the ground of

obviousness, reversing the jury verdict, I respectfully dissent. I must also dissent from the rejection of the jury verdict of infringement, for the district court applied a new and incorrect evidentiary standard that does not warrant ratification.

THE VALIDITY ISSUES

The jury's special verdicts upholding patent validity were sustained by the district court on post-trial motions. The defendants raised the ever-present multiple grounds of attack that appear in patent cases, and cross-appeal the jury verdicts on the issues of anticipation, indefiniteness, and obviousness, but do not appeal the verdicts for the plaintiff on the issues of inventorship, inequitable conduct, and antitrust violation. My colleagues reverse the jury verdict of unobviousness, and decline to reach the verdicts upholding validity on the issues of anticipation and indefiniteness. The district court sustained each of these verdicts. These issues were also raised for multiple reexaminations, and the PTO upheld patent validity on these grounds.

The teaching of Cardinal Chemical Co. v. Morton International, Inc., 508 U.S. 83, 97 (1993) ("[T]he Federal Circuit is not a court of last resort. If that court had jurisdiction while the case was pending before it, the case remains alive (barring other changes) when it comes to us. The Federal Circuit's determination that the patents were not infringed is subject to review in this Court, and if we reverse that determination, we are not prevented from considering the question of validity merely because a lower court thought it superfluous."),

strongly encourages our appellate review of the major issues that were decided and appealed, if such issues would be relevant to patent validity upon further proceedings in the Court. Review of the issues of validity that were litigated sheds further light on the nature of the invention; leaving these issues in silent limbo, despite the elaborate trial and appellate briefing and argument of these issues, distorts the context of the jury verdicts as well as the reexaminations. In this context I discuss the several issues of validity that are appealed, and explain why their judgment also warrants affirmance.

Anticipation

The jury found that the patents had not been proven invalid on the ground of anticipation. "Anticipation" means lack of novelty; that is, that the invention was already known. It is a factual question whose finding, when tried to a jury, is reviewed for support by substantial evidence on the record as a whole. Acromed Corp. v. Sofamor Danek Group, Inc., 253 F.3d 1371, 1378-79 (Fed. Cir. 2001); Advanced Display Sys. v. Kent State Univ., 212 F.3d 1272, 1281 (Fed. Cir. 2000).

A patent claim is deemed anticipated when every element and limitation of the claim is found in a single prior art reference, either explicitly or inherently. Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1368 (Fed. Cir. 2003). In order to anticipate, the reference must place a person who has ordinary skill in the field of the invention, in possession of the invention. See Akzo N.V. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1479 (Fed. Cir. 1986) ("anticipation requires

that each and every element of the claimed invention be disclosed in a prior art reference. In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public.")

The reference on which the defendants rely for anticipation is an article by Kenichi Koike entitled "Cryopreservation of Pluripotent and Committed Hemopoietic Progenitor Cells from Human Bone Marrow and Cord Blood," 25 Acta Paediatrica Japonica 275 (1983). Koike describes the preservation, by freezing in liquid nitrogen, of pluripotent and progenitor cells of bone marrow and umbilical cord blood, and shows that these cells retain much of their progenitor activity upon thawing. Koike does not mention stem cells, and states that "hematopoietic progenitor cells, especially pluripotent progenitor cells are the most important to repopulate the bone marrow." Id. at 276. Koike concludes with the suggestion that fetal cells or organs may be a source of progenitor cells for marrow transplantation, in the following statement:

> [T]he results that cord blood cells contain many pluripotent and nearby progenitor cells comparable to marrow cells, indicate that fetal hematopoietic cells or organs may be useful as one of the sources of hematopoietic progenitor cells for marrow transplantation.

Koike at 281.

The defendants argued at trial, and repeat on this appeal, that even if stem cells were not known or

shown by Koike to be present in umbilical cord blood, the claims are "inherently" anticipated by Koike because stem cells were present even if unknown. PharmaStem responded that inherent anticipation is avoided by lack of recognition, by lack of enablement, and by the limitations in the claims, including for the '681 claims the limitations to therapeutic compositions and the requirements that the cryopreserved cord blood units contain sufficient stem cells to reconstitute an adult. These aspects were extensively probed at the trial, and witnesses explained the various claim limitations and the prior art.

The district court, on post-trial motions, held that the jury verdict that the claims are not anticipated was supported by substantial evidence. The court referred to testimony of the expert witnesses for both sides, who agreed that Koike did not show hematopoietic reconstitution using cord blood, and that Koike did not enable transplantation. The defendant's expert witness testified (on cross-examination) that Koike's small samples could not contain a therapeutic amount of stem cells, and that the Koike article does not reflect knowledge of stem cells or indicate their presence to persons of skill in the field or show how to achieve transplantation of cord blood cells. As explained in In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985), possession of the invention adequate to show anticipation requires that a person of ordinary skill in the field of the invention would discern every element of the invention in the allegedly anticipating reference, and know how to carry it out based on the state of knowledge at the time of the reference. See, e.g.,

Elan Pharms., Inc. v. Mayo Found., 346 F.3d 1051, 1054 (Fed. Cir. 2003) (a claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled"). There was substantial evidence that Koike did not establish that there were stem cells in umbilical cord blood nor teach a therapeutic composition for use in hematopoietic reconstitution of a human adult.

The '681 patent describes the prior art in detail, including the following with respect to stem cells in human umbilical cord blood:

> A human hematopoietic colony-forming cell with the ability to generate progenitors for secondary colonies has been identified in human umbilical cord blood (Nakahata, T. and Ogawa, M., 1982, J. Clin. Invest. 70:1324-1328). In addition, hematopoietic stem cells have been demonstrated in human umbilical cord blood, by colony formation, to occur at a much higher level than that found in the adult (Prindull, G., et al., 1978, Acta Paediatr. Scand. 67:413-416; Knudtzon, S., 1974, Blood 43(3):357-361).

'681 patent, col. 4, lines 15-24. The '681 patent explains that the differences between stem and progenitor cells are operational and depend on functional rather than on morphological criteria. Col. 3, lines 4-39. In functional assays, stem cells can be identified by spleen colony forming units (CFU-S), whereas multipotent progenitor cells can be identified through colony-forming unit-granulocyte,

erythrocyte, monocyte/macrophage, megakaryocyte (CFU-GEMM) relatively differentiated progenitor cells through colony-forming unit-granulocyte, macrophage (CFU-GM) and burst-forming unit-erythroid (BFU-E). Id. at col. 26, lines 1-16. Koike, in determining the viability of the cryopreserved fetal bone marrow and cord blood, employed CFU-GM and BFU-E assays to measure progenitor cells, not stem cells.

The patent examiner concluded, and witnesses at trial testified, that the Koike reference is directed to progenitor cells, not stem cells. The re-examination record was in evidence, wherein the examiner stated:

> The remaining references that recited umbilical cord blood, specifically the Koike and Vidal references, recited the cryopreservation of a Ficoll-Hypaque fraction of umbilical cord blood and did not provide any evidence that viable human neonatal or fetal hematopoietic stem cells were present in the thawed samples.

Notice of Intent to Issue Reexamination Certificate at 4 (Jan. 11, 2000). The examiner observed that Koike did not mention stem cells and did not show or enable transplantation to an adult, and that although Koike postulated that cord blood may be a source of hematopoietic progenitor cells, Koike did not show how or if such use could be achieved. The examiner's reasons for allowance included the following:

> . . . Since hematopoietic stem cells engage in both replication and differentiation, the presence of progenitors (differentiated stem cells) is not predictive of the presence of stem cells. All of the prior art references which taught the cryopreservation of a Ficoli-Hypaque fraction of umbilical cord blood assayed for the presence of progenitor cells and merely theorized on the presence of stem cells. None of the prior art references demonstrated the presence of stem cells in the umbilical cord blood.

Id. When the reference relied on at trial was before the patent examiner, a reasonable jury may give weight to the examiner's view of the reference when deciding whether invalidity has been proved by clear and convincing evidence. See Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990) (referring to the particularly heavy burden in establishing invalidity on the same prior art that was examined in the PTO).

The defendants argue that it is irrelevant whether Koike described or recognized the presence of stem cells in cord blood, because they were inherently there. However, as discussed in Turbo Care Div. Of Demag Delaval Turbomachinery Corp. v. General Electric Co., 264 F.3d 1111, 1119 (Fed. Cir. 2001), "[i]n order for a disclosure to be inherent, 'the missing descriptive matter must necessarily be present in the [original] applicant's specification such that one skilled in the art could recognize such

a disclosure," (quoting Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998)). As the district court pointed out and as the expert witnesses testified, Koike does not show the claim limitations to therapeutic compositions or that the cryopreserved blood units must be from a single human or that stem cells must be present in an amount sufficient for hematopoietic reconstitution of a human adult, or suggest how to conduct a successful transplantation. Witnesses testified that persons in this field of science did not have the knowledge to routinely fill these omissions, and reinforce the examiner's statement that "the presence of progenitors (differentiated stem cells) is not predictive of the presence of stem cells." See Reexamination Notice of Intent, supra; see also Elan Pharmaceuticals, 346 F.3d at 1057 (discussing the need for evidence on the question of whether the reference placed a person of ordinary skill in possession of the invention as claimed); Rosco, Inc. v. Mirror Lite Co., 304 F.3d 1373, 1380 (Fed. Cir. 2002) ("Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element 'is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.") Particularly when the science or technology is new or complex, a bare suggestion or hope that requires significant experimentation for implementation or verification is not an invalidating "anticipation" of that which is ultimately achieved.

These aspects were explored at the trial, with witnesses for both sides agreeing that it was not

known, at the time of the Koike reference, how to use cord blood for marrow transplantation and human reconstitution. The district court concluded that a reasonable jury could have found that no single reference described all of the '681 patent claim limitations, explicitly or inherently. The panel should review this issue in the interest of finality, and rule that the verdict that anticipation of the '681 claimed invention had not been established was supported by substantial evidence, and was properly sustained by the district court.

The '553 claims are directed to method steps, including the step of introducing the stem cells into a human host. The district court summarized the evidence as follows:

> It is undisputed that Koike did not introduce cord blood into a human, which is a necessary limitation of the '553 Patent. The defendants claim that Koike's suggestion that introducing the stem cells into a human host should be done is a sufficiently enabling disclosure to warrant a finding of anticipation. Even so, the record contains substantial evidence from which a jury could find that a person of ordinary skill in the art would not have been so enabled.

PharmaStem, 2004 WL 2898061 at *4.

The defendants argue that Koike is as enabling as the patents in suit -- an argument that could well have been rejected by the jury, for the '681 patent describes extensive animal transplantation

experiments and shows surrogate assays of over one hundred cord blood units, and the '553 patent includes details of the transplantation of cryopreserved fetal cord stem cells to reconstitute the blood of a five-year-old child who was suffering from Fanconi's Anemia; in contrast with the absence of any such information in the Koike reference. The district court held that there was substantial evidence whereby a reasonable jury could have found that the Koike reference did not anticipate the '553 claims. I agree. The panel should review and resolve this issue, which was fully appealed, in the interest of finality.

Indefiniteness

A similar obligation applies to the cross-appeal of validity on the ground of indefiniteness. The matter was fully presented on the appeal to this court, and warrants resolution.

The defendants challenged both patents under 35 U.S.C. §112, arguing that the claims are indefinite because, at the time the patent applications were filed, stem cells in umbilical cord and placental blood could not be identified and the stem cell content could not be measured. The defendants' position is that measurement of stem cell content required actually transplanting the blood into a host and observing its effect, and that since the '681 composition claims require stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult," the defendants could not know if they were infringing the claims. PharmaStem's position is that surrogate animal tests, as shown in its patents, adequately measure

stem cell content. PharmaStem points out that the defendants all test the cord blood before placing it in storage and when releasing it for transplant. The jury found that the claims were not invalid on this ground, answering Question No. 10:

> Question No. 10
>
> Have the Defendants proven by clear and convincing evidence that the '681 patent is indefinite in that on November 12, 1987, a person of ordinary skill in the art would not have been able to determine from the patent what the claimed invention covers?
>
> YES ___ NO X

Witnesses explained at the trial that the '681 specification describes the conduct of surrogate assays and their use to test for stem cells, and correlates the surrogate assays with therapeutic stem cell effect. Reviewing the evidence, the district court referred to the expert testimony of Dr. Malcolm Moore, a cell biologist, that the patents provide "ample information to determine the amount of cord blood needed for transplant in adults and children, and that the scientific community has in fact performed numerous transplants into adults. Moore Tr. at 340-348." PharmaStem, 2004 WL 2898061 at *5.

Section 112 requires that the claims point out "the subject matter which the applicant regards as his invention," implementing the purpose of claims to identify what has been invented and found

patentable, so that "one skilled in the art would understand the bounds of the claim when read in light of the specification." Miles Laboratories, Inc. v. Shandon, Inc., 997 F.2d 870, 875 (Fed. Cir. 1993) ("If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more.")

The courts have recognized, particularly in fields of new and evolving knowledge, that the claims can be no more precise than the knowledge in the field permits. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1986) ("'if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more") (quoting Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624 (Fed. Cir. 1985)). See also, e.g., Marley Mouldings, Ltd. v. Mikron Indus., 417 F.3d 1356, 1361 (Fed. Cir. 2005) (when a claim "is not insolubly ambiguous, it is not invalid for indefiniteness"); Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) ("if the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds"). The defendants argue that even if this criterion is met, it is inadequate to satisfy § 112 in this case because the defendants had no way of being certain whether any unit of cord blood infringed the claims. The defendants argue that even if the science later

evolved so that stem cell content could be directly measured, such information did not exist when the '681 application was filed.

To patent an invention when the science or technology to which it is directed is incompletely developed or understood, requires that it be described and claimed in terms adequate to communicate, to persons experienced in the field of the invention, what has been discovered. The '681 patent states that "any of numerous assays for hematopoietic stem or progenitor cells may be used." Col. 25, lines 49-50. For example:

> [A]n item cell assay for CFU-S (colony forming unit-spleen) can be done. In this assay, cells considered to be multipotential stem cells with self-renewal capacity can be measured by counting the number of colonies (nodules) on the spleen(s) of lethally-irradiated mice that have been inoculated with a composition containing the cells.

Col. 26, lines 1-7. The CFU-S assay is done essentially the same way as progenitor cell assays such as BFU-E/CFU-GEMM and CFU-GM assays. Col. 48, lines 42-43. The specification states:

> A survey of published reports indicates that the number of CFU-GM infused for autologous bone marrow reconstitution in human patients, can be relied on as an indicator of the potential for successful hematopoietic reconstitution

> (Spitzer, G., et al., 1980, Blood 55(2): 317-323; Douay et al., 1986, Exp. Hematol. 14:358-365). By standardizing published data by patient weight, and assuming a patient weight of 150 pounds (67.5 kilograms), the calculated number of CFU-GM needed for successful hematopoietic reconstitution using autologous bone marrow cells ranges from 2-425x10^4, with faster recovery noted using greater than 10x10^4 CFU-GM.

Col. 50, line 64 to col. 51, line 8. The expert testimony at trial explained this and other descriptive text, whereby a reasonable jury could have concluded that the assays described in the patent serve to ascertain whether sufficient amounts of stem cells are present in the preserved cord blood to reconstitute the host.

It was not disputed that the information in the specification is as definite as the state of scientific knowledge at the time of filing. It has been recognized that the "existence of an inescapable area of uncertainty is not sufficient justification for denying to the patentee the fruits of his invention." Ga. Pac. Corp. v. U.S. Plywood Corp., 258 F.2d 124, 136 (2d Cir. 1958) ("the policy of the patent statute contemplates granting protection to valid inventions, and this policy would be defeated if protection were to be accorded only to those patents which were capable of precise definition. The judicial function requires a balancing of these competing considerations in the individual case.") The district

court fulfilled this judicial function, stating, in denying the defendants' motion for JMOL, that: "Given that there is no determinate or determinable minimum amount of cord blood for therapeutic usefulness in humans, the record supports that the '681 claim language is as precise as the subject matter permits." PharmaStem, 2004 WL 2898061 at *5 (citing Hybritech, supra). As the district court ruled, there was substantial evidence whereby the jury could have found that the claims of the '681 and '553 patents would be understood by persons in the field of the invention. The verdict that the claims are not invalid for indefiniteness should be sustained, and should be reviewed, not left dangling on appeal.

Obviousness

The ultimate solution of a previously intractable problem can indeed appear to become apparent in hindsight after the final successful step is taken. Yet that final step in this case was not taken by those who came before, and was clearly not "obvious" to contemporaries, who acclaimed the achievement. Even the defendants' expert witness acknowledged that before the work of these inventors "stem cells could not be conclusively proved to be present in cord blood." Maj. op. at 42. Nonetheless this court rejects the testimony and admissions of the defendants, and uses present knowledge of the inventors' success to find that it was obvious all along.

When trial is to a jury, the court instructs the jury as to the applicable law, and the jury applies the law to the facts as it finds them. Appellate review is

on the standard of determining whether there was substantial evidence to support the jury's express or presumed factual findings, and whether the jury applied the correct law to those findings. See C.R. Bard, Inc. v. M3 Systems, Inc., 157 F.3d 1340, 1351-52 (Fed. Cir. 1998) ("We review a jury verdict of obviousness to determine whether substantial evidence supports the factual findings predicate to the legal conclusion of obviousness and whether such findings can support the verdict, with appropriate consideration of the presumption of validity and the requirement that obviousness be proved by clear and convincing evidence; factual inferences are drawn and credibility determinations are accepted in favor of the verdict winner.") The question is whether the jury's verdict is sustainable on the evidence presented, not whether we could have or would have gone the other way on the evidence presented.

The jury answered "NO" to the question whether the '681 and '553 claimed inventions "would have been obvious to a person of ordinary skill in the field of the invention." Responding to the defendants' challenge to the verdict, PharmaStem points to the evidence of the extensive research in this field of science -- much of which is set forth in the patent specifications -- and to the specific claim limitations. The broadest composition claim (the '681 patent) is as follows:

> 1. A cryopreserved therapeutic composition comprising:
>
> viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental

> blood of a single human collected at the birth of said human,
>
> in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult;
>
> and an amount of cryopreservative sufficient for cryopreservation of said cells.

This claim was the subject of two reexaminations, one preceding this litigation, the second completed during the past year. For the first reexamination, the examiner's reasons for allowance included the following:

> The claims as amended now avoid the prior art for the following reasons. First, it was noted that the only piece of prior art which taught a composition which could have combined an amount of viable human neonatal or fetal hematopoietic stem cells sufficient to effect hematopoietic reconstitution of a human adult was the reference of Ende. The Ende reference, published in 1972, recited the treatment of an individual undergoing treatment for leukemia who received a series of cord blood infusions from multiple donors and showed a transient change in red blood cell phenotype. Even though the authors of the Ende article describe the procedure as "transplantation," it is clear that

> such treatment did not result in hematopoietic reconstitution. Further, since no HLA typing was performed, and multiple infusions were performed, one of ordinary skill in the art would have taken the disclosure of Ende to be equivalent to blood transfusions and would have had no expectation that the hematopoietic reconstitution of a human adult could have been performed. As a transfusion composition, one of ordinary skill would have had no motivation to cryopreserve the cord blood, since whole blood for transfusion is not frozen, but stored st 4°C and Ende further points out that any hospital with a maternity ward would provide sufficient aliquots of fresh cord blood.

Notice of Intent to Issue Reexamination Certificate at 3-4 (Jan. 11, 2000). The examiner discussed the state of the science, the content of the prior art, the known sensitivity of fetal liver and thymus stem cells to freezing, and the unpredictability of this field, and concluded:

> This disclosure combined with the acknowledged sensitivity of hematopoietic stem cells from fetal liver and thymus to cryopreservation and the fact that DMSO is toxic to fetal liver progenitor cells at concentrations nontoxic to bone marrow cells provides an unpredictability in the art of

> cryopreservation of stem cells from different sources that renders the suggestions of the prior art references as to the therapeutic uses of umbilical cord blood (whether cryopreserved or not) as a course of hematopoietic stem cells a situation of "obvious to try," which fails to provide a prima facie finding of obviousness . .

Id. at 4.

For the second reexamination, the examiner discussed additional arguments involving the same references on which this court now relies to invalidate the patent:

> At the time of the instant invention the use of cord blood for hematopoietic reconstitution had never been accomplished. Additionally, in vitro expansion of cord-blood stem cells prior to patient implantation had not been successfully employed, and indeed is not in use as of today as indicated by the Dr. Zander declaration. Accordingly, determination of a pharmaceutically efficacious and safe dosage that results in human adult hematopoietic reconstitution would necessarily require undue experimentation, thus precluding enablement. In this respect, it was patentee's in vitro progenitor assays taken in conjunction with in vitro mice testing showing hematopoietic reconstitution with a relatively small

> amount of neonatal blood, that provided the necessary teaching to enable the obtaining of effective hematopoietic reconstituting dosages in children (extrapolatable to adults) by utilizing cord blood volumes (50-100 ml) derived from a single adult. Thus, neither the Koike reference taken alone anticipates, nor a combination of references render obvious, the instantly claimed invention.

Reexamination -- Reasons for Patentability/Confirmation (Dec. 29, 2006). No error has been shown in this analysis, which warrants deference in accordance with the strictures of the Administrative Procedure Act. See Dickinson v. Zurko, 527 U.S. at 164 ("A reviewing court reviews an agency's reasoning to determine whether it is "arbitrary" or "capricious," or, if bound up with a record-based factual conclusion, to determine whether it is supported by "substantial evidence."), citing SEC v. Chenery Corp., 318 U.S. 80, 89-93 (1943).

The record contains testimony that scientists working in the field of hematopoietic reconstitution did not expect cord blood to be a successful transplant tissue or a useful source of hematopoietic stem cells. There was testimony that earlier efforts at using cord blood had encountered problems, and that there was skepticism and surprise at the inventors' achievement. The reaction of scientific peers after the achievement is relevant to whether the invention would indeed have been obvious at the time it was made. See Cardiac Pacemakers, Inc. v.

St. Jude Medical, Inc., 381 F.3d 1371, 1376 (Fed. Cir. 2004) (evidence of skepticism that the multi-mode treatment of the invention could be achieved supported the jury verdict of nonobviousness); Metabolite Laboratories, Inc. v. Laboratory Corp. of America Holdings, 370 F.3d 1354, 1368 (Fed. Cir. 2004) (evidence that skilled artisans were initially skeptical about the invention supported the jury's verdict of nonobviousness).

The significance of the inventors' work was in evidence, including their founding of Biocyte and spawning of the industry of collecting and cryofreezing umbilical cord blood. In evidence was defendant ViaCord's "business plan" which identified these inventors as "the trailblazers":

> The founding scientists are core researchers in this field and have published many related articles. Biocyte's time, energies, and financial resources have been spent doing much education and development in this field. They are the trailblazers.

A communication to these inventors from the founder of defendant Cryo-Cell stated:

> [N]o one will ever dispute that you, as the pioneers in the medical technology ... will be the frontrunners in the field of utilizing of the blood from the umbilical cord for restoring hematopoietic through marrow transplants.

Such evidence assists in replacing judicial hindsight with objective determination as of the time of the invention. See Vandenberg v. Dairy Equip. Co., 740 F.2d 1560, 1567 (Fed. Cir. 1984) (in "determining the question of obviousness, inquiry should always be made into whatever objective evidence of nonobviousness there may be"). In Graham v. John Deere Co, 383 U.S. 1, 17-18, 36 (1966) the Court counseled that "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., "serve to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue," cited in KSR v. Teleflex, 127 S. Ct. at 1734.

PharmaStem's expert, Dr. Bernstein, testified that no prior art showed that cord blood contains stem cells, and that persons of skill in this field would not have had a reasonable expectation of success in carrying out the claimed process. Dr. Bernstein also discussed the early uncertainties and mistaken understanding concerning stem and progenitor cells. His testimony is now disputed by this court, denying it the weight that a reasonable jury could have given it. Dr. Bernstein had explained at the trial that at the time of filing the patent application the differences between stem cells and progenitor cells could not be measured and were not well understood. The jury could have accepted this testimony, and indeed the defendants did not refute it; but the panel majority now holds that the inventors' apparently inconsistent use of stem and progenitor terminology constitutes an "admission in the specification regarding the prior art" which is

then "binding on the patentee for purposes of a later inquiry into obviousness." Maj. op. at 42. This is not a simple issue, but the jury could reasonably have concluded, as did the district court, that the prior art did not show that there were stem cells in cord blood, and that one of ordinary skill in this field would not have had a reasonable expectation of successful use of cord blood to reconstitute a human adult.

A reasonable jury could have found that these inventors were not simply conducting a routine optimization, as my colleagues now rule on what they describe as the "more difficult question [of] whether the prior art would have given rise to a reasonable expectation of success in creating the [claimed inventions]." My colleagues state that they are "plainly satisfied" that "a person of ordinary skill in the art would have had reason to attempt to make [the claimed inventions]." I agree that there was reason to seek a cure for destroyed blood cells, and that scientists have been seeking such a cure for a long time, including those scientists whose work is the cited prior art. There has been much hopeful speculation about the potential of stem cells, although this remedy eluded those who came before.

It is often far easier to recognize the problem than to find and demonstrate the solution. The patent law recognizes that advances of great power may be based as much on persistent and skilled investigation as on the flash of creative genius, for both serve to transcend that which was previously achieved. See 35 U.S.C. § 103 ("Patentability shall not be negatived by the manner in which the invention was made.") My colleagues go too far in

limiting the patent system to the serendipitous and the unexpected. Maj. op. at 35 ("while their work may have significantly advanced the state of the science of hematopoietic transplantations by eliminating any doubt as to the presence of stem cells in cord blood," they "merely used routine research methods to prove what was already believed to be the case"). Further, these scientists not only established the presence of stem cells, but also enabled their development for preservation and hematopoietic reconstitution.

The court's approach reflects misperception of the scientific process as well as the patent purpose. Scientific methodology usually starts with a hypothesis based on what is already known; the record shows that several scientists mentioned the idea of rebuilding destroyed blood cells. However, none achieved this long-sought goal, and the record shows the extreme skepticism concerning even the possibility of this achievement. The district court found that there was "tremendous skepticism in the transplant field regarding the use of cord blood as a transplant tissue," and that the jury could have found that "prior to the inventions of the Patents-in-suit, those in the field of hematopoietic reconstitution would not have expected cord blood to be a successful transplant tissue."

Nonetheless, my colleagues deny the value of this long-sought result, whereby for the first time umbilical blood was preserved and recovered and used to reconstitute the hematopoietic systems in mammals, demonstrated with the mice experiments reported in the '681 patent, and the human

transplant in the '553 patent. Not even the defendants denigrate the inventors' achievement as "merely supporting evidence" for an "expected" result, as in the maj. op. at 39. Even if this court were not required to recognize the substantial evidence in support of the jury verdict, even if APA deference were not required to the three PTO reexaminations, one must pause at the powerful evidence of the acclaim that was accorded to this achievement, by these defendants as well as by scientific peers.

There was substantial evidence whereby the jury could have sustained the unobviousness of the '681 and '553 inventions. I must, respectfully, dissent from the panel majority's invalidation of these patents on this ground.

INFRINGEMENT

The jury found infringement of the '681 and '553 patents. In determining whether substantial evidence supported the verdict, the evidence before the jury and all reasonable inferences therefrom must be viewed in the light that is favorable to the verdict, without substituting the court's view of the evidence for that of the jury. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 254-55 (1986); see SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1355 (Fed. Cir. 2000) ("In reviewing the record, we must draw all reasonable inferences in favor of the prevailing party, and not make credibility determinations or substitute our view of the conflicting evidence for that of the jury.") My colleagues, like the district court, grant JMOL on a ruling of law and evidence that was not presented to

the jury, and that in all events does not support reversal of the verdict.

My colleagues appear to hold that infringement cannot be found because the cryopreserved cord blood "relates only as possibilities" for "future use in adult transplants." Indeed, this entire system is designed for possible future needs of the infant itself or family members. The defendants' testimony was uniformly to the effect that this "possibility" was the purpose of their preservation service (the record also describes a case in which the cord blood was used to treat the mother's existing disease). The evidence was that most but not all of the cryopreserved cord blood that has been transplanted was to children, with about ten percent transplanted to adults. PharmaStem is correct that this ratio relates to damages, and does not simply serve to negate all liability for infringement.

The district court ruled that PharmaStem had not proved infringement because PharmaStem did not separately analyze the stem cell content of each sample of cord blood. PharmaStem presented evidence that separate analysis was unnecessary because each defendant had analyzed each sample before accepting it for storage. Every defendant testified that the blood it collected and stored was analyzed for cell content at the time of collection. The jury was not instructed that such evidence was inadequate and inadmissible -- as the district court ruled post-trial. On the evidence presented, this is not a sound basis for rejecting the jury's verdict. The tardy rejection of the testimony of PharmaStem's expert witness, Dr. Hendrix, is an inappropriate

application of Daubert and its succeeding cases, on which the panel majority relies, for there was no criticism of the expert's scientific credentials or her analysis of the prior art and the state of the science. See Daubert v. Merrell Dow Pharms., 509 U.S. 579, 590 (1993) (for a scientific assertion to "qualify as 'scientific knowledge,' an inference or assertion must be derived by the scientific method"); Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999) (the principles of Daubert apply broadly to "scientific, technical, or other specialized knowledge").

The district court's ground of exclusion was not that Dr. Hendrix made an error of law or of scientific fact, but simply that she also stated her opinion concerning the defendants' marketing statements that they test and preserve cord and neonatal blood for possible future child and adult use -- testimony that the district court criticized because it did not require scientific expertise. Whatever the virtue of that criticism, it is clear that the district court's (and my colleagues') exclusion of the entire testimony of this eminent scientist on this ground is not what the Daubert ruling is about. There was no testimony contrary to the view of Dr. Hendrix of the scope of the representations made in the marketing materials, and no challenge to the accuracy of her statements. Presentation of expert testimony was in compliance with the general rule that "typically expert testimony will be necessary in cases involving complex technology," Centricut, LLC v. Esab Group, Inc., 390 F.3d 1361, 1370 (Fed. Cir. 2004), and this expert's testimony did not cross the boundaries of admissibility.

The '681 Patent

The district court granted JMOL of non-infringement of the '681 patent on the ground that PharmaStem had not proved that 100% of the defendants' preserved cord and neonatal blood contained sufficient stem cells to reconstitute an adult. The district court reasoned that since PharmaStem took the litigation position that it was entitled to damages measured as a royalty based on 100% of the preserved blood, to prove infringement PharmaStem had to prove that 100% of the preserved blood contained sufficient stem cells to provide adult reconstitution, by analyzing 100% of the preserved blood. As I have mentioned, Pharma-Stem complains that this criterion differed from that on which the jury was instructed, and also states that even this criterion was met by substantial evidence presented at the trial.

My colleagues, overturning the jury verdict, hold that there is no infringement of the '681 patent because PharmaStem did not retest every unit of stored blood to determine its stem cell content. They ignore the evidence that every unit was tested by each defendant before being placed into cryogenic storage; every defendant so testified. It was not disputed that retesting of every unit could use up a significant amount of the precious preserved blood. No defendant asserted that it routinely cryogenically preserved cord blood that did not contain sufficient stem cells to be potentially useful for hematopoetic reconstitution. A reasonable jury could have considered this evidence to find that each element of the claims was met. Instead, my colleagues simply

rule that without testing of the stored units there can be no liability at all. That evidentiary theory was not presented to the jury; it is too late to criticize as legally inadequate the testimony that was based on the defendants' own representations concerning the content of the stored umbilical and neonatal blood.

The verdict of infringement was supported by the defendants' own testimony setting forth their requirements for stem cell content before accepting cord blood for cryopreservation. For example, defendant CBR's Scientific Director testified that every unit of cord blood presented to CBR for storage is tested to see if it contains a sufficient amount of stem cells to have "a good probability of being useful in the clinical setting." In evidence were CBR's website statements that "transplants have occurred for the newborn himself, the newborn's mother, father, and the newborn's cousin," and "umbilical cord blood from unrelated donors can restore hematopoiesis in adults who receive myeloablative therapy and associated with acceptable rates of severe acute and chronic GVHD [Graft vs. Host Disease]."

The President of defendant CorCell testified that "what our marketing materials state [is] that it may be used to treat the donor or siblings or potentially parents," and that although only one CorCell stored cord blood unit had thus far been transplanted, that transplant was to an adult. There was testimony that CorCell's cord blood samples are tested for "total nucleated, CD-34+ and viability cell counts before and after processing," and "a colony-

forming assay is conducted to evaluate the quality and quantity of umbilical stem cells," and that a sample is usually not preserved if its stem cell content is determined to be unsuitable for possible future use. The jury was shown CorCell's representation to investors that "a recent study of twenty-five (25) patients, published in the New England Journal of Medicine, similarly indicates that cryopreserved umbilical cord blood stem cells can be successfully engrafted in children and adults with a variety of hematologic or immunologic disorders." The jury saw evidence that CorCell defines potential recipients of the stored stem cells as "the family members of the newborn, mother, father, siblings and possibly grandparents."

Defendant ViaCell's founder testified that each cord blood sample was tested to ensure that there is a sufficient amount of stem cell content to be therapeutically useful, as determined by ViaCell's Scientific Advisory Board. ViaCell's Senior Vice President testified that ViaCell counts the cells in every collected sample, and that its standard procedure states: "A minimum total NC count of 3.0 x 10^8 is required to proceed with processing." A ViaCell memorandum to investors stated that about 10% of all cord blood transplants were in adults, and a ViaCell witness testified that ViaCell informs the public about adult use.

At the trial none of the defendants denied the stem cell content of the blood they cryopreserved, other than to state that for the few cases where their analysis at collection showed weak stem cell content they would consult with the infant's family before

accepting and freezing the blood. The jury heard the defendants' testimony and unqualified representations concerning their screening of every stored sample of cord blood for stem cell content, and that they did not distinguish between potential child and adult use of the stem cells. The jury could have relied on the defendants' testimony that their minimum threshold for cryopreservation is sufficient stem cells for transplantation, and that all of the defendants included possible adult use in their publicly-stated reasons for storing fetal cord and neonatal blood. PharmaStem points out that it was neither necessary nor prudent to test each unit of the defendants' stored blood for stem cell content, when each defendant had already done so.

The jury was instructed: "A defendant is liable for directly infringing PharmaStem's patents if you find that PharmaStem has proven by a preponderance of the evidence that they have made, used, offered for sale or sold a composition that includes each and every element of at least one of the asserted claims of the '681 patent." The theory that each stored sample had to be separately analyzed by PharmaStem to show infringement was not presented as law to the jury. This was a new standard for infringement, for the jury was not told that the defendants' analyses of stem cell content could not provide evidence of stem cell content.

When there is substantial evidence in support of the jury's verdict, it is irrelevant whether the appellate court would have preferred different or additional evidence. "When the jury is supplied with sufficient valid factual information to support the

verdict it reaches, that is the end of a matter . . . . the jury's factual conclusion may not be set aside by a JMOL order." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1355 (Fed. Cir. 2001). The district court erred in holding that it was necessary for PharmaStem to analyze, or provide detailed analysis results, for the individual blood units in order to find infringement. My colleagues commit the same error, reweighing the evidence to reach their preferred result, rather than considering whether substantial evidence as presented at the trial supports the verdict that was reached by the jury.

The '553 Patent

It was agreed at trial that the claims of the '553 patent are not infringed until the step of transplanting the stem cells takes place. Since relatively few transplants of stored blood had been done, the royalties awarded by the jury were modest, and were not appealed. However, the verdict of infringement is supported by substantial evidence, and should stand. There was substantial evidence that each step of the claimed invention is performed by the defendants followed by a transplant surgeon. Referring to claim 13, the defendants isolate the umbilical cord and placental blood containing stem cells and cryopreserve it in liquid nitrogen; claim clauses (a) and (b). When instructed on behalf of the donor or family members, the blood is delivered to a surgical environment where it is thawed, claim clause (c), and transplanted into the human host, claim clause (d):

13. A method for hematopoietic or immune reconstitution of a human comprising:

(a) isolating human neonatal or fetal blood components containing hematopoietic stem cells;

(b) cryopreserving the blood components;

(c) thawing the blood components; and

(d) introducing the blood components into a suitable human host, such that the hematopoietic stem cells are viable and can proliferate within the host.

The jury found the defendants liable for "acting in concert or working together" with the transplant physicians, or contributing to the infringement of the '553 patent, upon answering the following questions:

Question No. 3: Substantial Non-Infringing Use

Has PharmaStem proven by a preponderance of the evidence that cryopreserved cord blood has no substantial noninfringing use?

YES X NO ____

Question No. 4: Direct Infringement

Has PharmaStem proven by a preponderance of the evidence that defendants and the transplant physicians are acting in concert or working together to complete the process of infringement of claims 13, 19, 47, 53, or 57 of the '553 patent by performing each and every one of the steps in any of those claims?

YES X NO ____

Question No. 5: Contributory Infringement

Has PharmaStem proven that a defendant has contributorily infringed the '553 patent by selling or offering to sell cryopreserved cord blood that was actually used by a third party in the direct infringement of any of claims 13, 19, 47, 53, or 57 of the '553 patent?

Answer separately for each defendant.

ViaCell	YES	X	NO	____
CBR	YES	X	NO	____
Cryo-Cell	YES	X	NO	____
CorCell	YES	X	NO	____

PharmaStem thus received special verdicts of both direct joint infringement and contributory infringement. My colleagues grant JMOL on the ground that since the defendants are providing a

service, not selling a product, they can not meet the "sale" requirement of contributory infringement, 35 U.S.C. § 271(c).[1] PharmaStem points out that a reasonable jury could have found that the defendants sell (rent) their blood-storage facilities to the donor's family, and that the defendants either contribute to or act in concert with the transplanting surgeon to practice the claimed method.

The principles of patent infringement are not negated when the steps of a method claim are performed by more than one entity. There was no instruction as to legal impossibility of liability as to the '553 patent, and no objection was raised to the verdict questions. We are not told whether the legal theory of sale or rent was aired at the trial, but it is apparent that the jury was fully apprised of the nature of the accused activities, as reflected in the jury questions. The processes of litigation require appellate review on the premises of the jury trial, lest invited error dominate trial tactics.

No objection was raised to the jury instructions. The distinction relied on by the panel majority, that the defendants were bailees, not sellers, does not negate the principles of infringement, whether viewed as joint infringement

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[1] 271(c). Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

or contributory infringement. See, e.g., On Demand Machine Corp. v. Ingram Indus., Inc., 442 F.3d 1331, 1334 (Fed. Cir. 2006) (approving instruction that "It is not necessary for the acts that constitute infringement to be performed by one person or entity.") PharmaStem is correct that the issue to which this evidence applies relates to damages, not infringement, and points to the small amount of damages awarded for infringement of the '553 patent (damages for the '553 patent were not appealed by the defendants).

It is irrelevant whether any steps of a method claim can be viewed as a "service;" infringement requires only that the steps be performed. As discussed in Dawson Chemical Co. v. Rohm and Haas Co., 448 U.S. 176, 188 (1980), the purpose of the contributory infringement statute is "to protect patent rights from subversion by those who, without directly infringing the patent themselves, engage in acts designed to facilitate infringement by others," a criterion that the jury could have found was met by the facts and relationships of this case. On the instructions to the jury, the verdict of liability for contributory or joint infringement of the '553 patent is supported by substantial evidence, and should be sustained.

From the court's departure from the procedures of appellate review of jury verdicts, and from the flawed law that is propounded, I must, respectfully, dissent.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

PHARMASTEM THERAPEUTICS, INC. Plaintiff, v. VIACELL INC., et al., Defendants.	C.A. No. 02-148-GMS

Philip A. Rovner, of Potter Anderson & Corroon LLP, Wilmington, Delaware, for Plaintiff, Paul J. André, Lisa Kobialka, of Perkins Coie LLP, Menlo Park, California, of counsel.

Jeffrey L. Moyer, of Richards Layton & Finger, Wilmington, Delaware, Richard D. Kirk, of Morris James Hitchens & Williams LLP, Wilmington, Delaware, and Robert F. Stewart, of Dilworth Paxson LLP, Wilmington, Delaware, for Defendants, Paul F. Ware, John C. Englander, James C. Rehnquist, James W. McGarry, and Elaine Herrmann Blais, of Goodwin Procter LLP, Boston, Massachussetts; William F. Abrams, Thomas F. Chaffin, and Randal Ivor-Smith, of Pillsbury Winthrop LLP, Palo Alto, California; and James L. Rodgers, Evelyn H.

McCarthy, and Lisa Burgin Conte, of Dilworth Paxson LLP, Philadelphia, Pennsylvania, of counsel.

MEMORANDUM OPINION

September 15, 2004
Wilmington, DE

SLEET, District Judge

I. INTRODUCTION

On February 22, 2002, PharmaStem Therapeutics, Inc. ("PharmaStem") filed suit against ViaCell, Inc. ("ViaCell"), Cryo-Cell International, Inc. ("Cryo-Cell"), CorCell, Inc. ("CorCell"), StemCyte, Inc. ("StemCyte"), CBR Systems, Inc. ("CBR"), Birthcells Technology, Inc. ("Birthcells"), Nustem Technologies, Inc. ("Nustem"), and Bio-Cell, Inc. ("Bio-Cell") (collectively "ViaCell" or "the defendants"),[1] alleging infringement of United States Patents Nos. B1 5,004,681 ("'681 Patent") and 5,192,553 ("'553 Patent") (collectively "the Patents-In-Suit"). The Patents-In-Suit are generally directed toward cryopreserved therapeutic compositions containing hematopoietic stem cells obtained from umbilical cord or placental blood of a newborn, the '681 Patent, and methods pertaining to the therapeutic use of such compositions, the '553 Patent.

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[1] A default judgment was subsequently rendered against NuStem on July 10, 2002. StemCyte and PharmaStem entered a settlement agreement before trial, and StemCyte accordingly was dismissed from this action on October 21, 2003.

ViaCell asserted the defenses of invalidity for anticipation, indefiniteness, inequitable conduct and obviousness. The court held a *Markman* hearing and issued an order construing the disputed terms of the '681 and '553 Patents on January 13, 2003. A jury trial commenced on October 10, 2003. During trial, both parties properly moved for judgment as a matter of law ("JMOL") pursuant to Rule 50(a) of the Federal Rules of Civil Procedure. The court reserved ruling on all JMOL motions.

On October 29, 2003, the jury returned a unanimous verdict on all claims in favor of PharmaStem. The jury found that each of the defendants infringed the claims of the '681 and '553 Patents, and that each of the defendant's infringement of those patents was willful. The jury also upheld the validity and enforceability of the Patents-In-Suit, found that PharmaStem did not commit any anti-trust violation, and awarded PharmaStem past damages in the amount of $7,126,544.92. The court entered judgment on the verdict on October 30, 2003.

Following the jury's verdict, ViaCell filed a renewed motion for judgment as a matter of law, and, in the alternative, a motion for a new trial or for a remittitur. Defendants CBR, CorCell, and Cryo-Cell joined in Viacell's motions and submitted individual memoranda addressing issues specific to each of them. ViaCell filed another alternative motion, in which the three other defendants also joined, for findings by the court and/or to alter or amend judgment pursuant to Federal Rule of Civil Procedure 52, 59(e) and/or the court's equitable power. PharmaStem filed a motion for enhanced

damages, attorneys' fees, pre-judgment interest and post judgment interest, a motion for a permanent injunction, as well as a motion to strike the affidavit of Chris Adams submitted in support of ViaCell's motion to alter or amend the judgment. Addressing these motions collectively herein, the court will enter judgment as a matter of law that defendants do not infringe the '553 patent and grant a partial new trial on the issue of infringement of the '681 Patent.

II. STANDARDS OF REVIEW

A. Renewed Motion for Judgment as a Matter of Law

Pursuant to Federal Rule of Civil Procedure 50, a court may render judgment as a matter of law after the moving party is fully heard on an issue at trial, if "there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." *Walter v. Holiday Inns, Inc.*, 985 F.2d 1232, 1238 (3d Cir. 1993) (citation omitted). If the court denies a motion for JMOL during trial, the motion may be renewed within ten days of entry of judgment in the case. FED R. CIV. P. 50(b). To prevail on a renewed motion for JMOL following a jury trial, a party "'must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusion(s) implied [by] the jury's verdict cannot in law be supported by those findings.'" *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1348 (Fed. Cir. 1998) (quoting *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893 (Fed. Cir. 1984)). "'Substantial' evidence is such relevant evidence from the record taken as a whole as might be accepted by a

reasonable mind as adequate to support the finding under review." *Perkin-Elmer Corp.*, 732 F.2d. at 893. In assessing the sufficiency of the evidence, the court must draw all reasonable inferences from the evidence in the light most favorable to the nonmovant. *Id.; Richardson-Vicks Inc. v. UpJohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The appropriate inquiry is whether a reasonable jury, given the facts before it, could have arrived at the conclusion it did. *Dawn Equip. Co. v. Kentucky Farms, Inc.*, 140 F.3d 1009, 1014 (Fed. Cir. 1998). The court may not determine the credibility of the witnesses nor "substitute its choice for that of the jury between conflicting elements of the evidence." *Perkin-Elmer Corp.*, 732 F.2d at 893.

B. Motion for a New Trial

The court may grant a new trial pursuant to Federal Rule of Civil Procedure 59 "for any of the reasons for which new trials have heretofore been granted in actions of law in the courts of the United States." FED. R. CIV. P. 59(a). A court should grant a new trial in a jury case, however, only if "the verdict was against the weight of the evidence ... [and] a miscarriage of justice would result if the verdict were to stand." *Williamson v. Consolidated Rail Corp.*, 926 F.2d 1344, 1352 (3d Cir. 1991). In making this determination, the trial judge should consider the overall setting of the trial, the character of the evidence, and the complexity or simplicity of the legal principles which the jury had to apply to the facts. *Lind v. Schenley Industries, Inc.*, 278 F.2d 79, 89 (3d Cir.), *cert. denied*, 364 U.S. 835 (1960)

III. DISCUSSION

A. Defendants' Renewed Motion for Judgment as a Matter of Law

1. The Jury's Verdict That the Patents-In-Suit Are Not Obvious, Anticipated or Indefinite Is Supported by Substantial Evidence.

a. Obviousness

The defendants contend that both the '681 and '553 Patents are invalid as obvious under 35 U.S.C. § 103. Whether or not a patent is obvious over the prior art is a question of law. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1479, 1479 (Fed Cir. 1997); *see also Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384-85 (Fed Cir. 2001). Section 103 provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S. § 103. Put simply, an invention is invalid if "the difference between the new thing and what was

known before is not considered sufficiently great to warrant a patent." *Graham v. John Deere Co.*, 383 U.S. 1, 15 (1966). Obviousness cannot be based on "the hindsight combination of components selectively culled from the prior art to fit the parameters of the invention." *ADT Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed Cir. 1998). The Supreme Court has set forth four factors relevant to determining obviousness: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) other secondary considerations. *Graham*, 383 U.S. at 17-18. Evaluating the *Graham* factors in view of the evidence adduced at trial, it was not unreasonable for the jury to have concluded that the Patents-In-Suit were not obvious.

Indeed, PharmaStem proffered ample evidence to support the jury's verdict. Both a suggestion to make the composition or carry out the claimed process and a reasonable expectation of success must be found in the prior art to support a conclusion that a patent is obvious. *See In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). At trial, PharmaStem presented testimony that there were problems associated with transplant tissues used prior to the Patents-In-Suit. Bernstein Tr. at 2035-2038. There was also tremendous skepticism in the transplant field regarding the use of cord blood as a transplant tissue, Bernstein Tr. at 2043-204, and the references ViaCell asserts (namely Koike, Knudtzon and Vidal) did not overcome this skepticism. Bernstein Tr. at 2045-2048, 2054-2060. Finally, testimony established that those in the field of transplantation were surprised at the result of the first cord blood

transplant conducted by the inventors of the Patents-In-Suit. Bernstein Tr. at 2061-2062. *See also* Wagner Tr. at 1378-1379. It is true that ViaCell capably highlights record evidence as to the meaning one of ordinary skill would attach to the alleged prior art references. Base upon the record evidence, a jury could have found that the Patents-In-Suit were obvious. This jury, however, did not, and the aforementioned evidence provided it with sufficient basis to reach the conclusion that, prior to the inventions of the Patents-In-Suit, those in the field of hematopoietic reconstitution would not have expected cord blood to be a successful transplant tissue.

The jury also received an abundance of evidence to support the secondary considerations of long felt need, commercial success, failure of others, copying, and unexpected results. See *e.g.*, Bernstein Tr. at 2036, 2060-2061; Wagner Tr. at 1187; Tr. Ex. 413. Additionally, with respect to the '681 patent, the jury was permitted to consider the fact that the Patent and Trademark Office ("PTO") considered the alleged prior art in the reexamination and ultimate reissue of that patent. Similarly, during examination of the '553 Patent, the PTO considered the Ende, Prindull, and Knudtzon references, a fact which the jury was also entitled to consider in evaluating their combined effect on the obviousness issue. The court is not to "substitute its choice for that of the jury between conflicting elements of the evidence." *Perkin-Elmer Corp.*, 732 F.2d at 893. In view of this standard, there is no basis to overturn the jury's finding that the Patents-In-Suit are not obvious.

b. Anticipation

Likewise, the jury's finding that the Patents-In-Suit are not invalid for anticipation is supported by substantial evidence. The defendants first contend that the '681 patent is anticipated by Koike because the latter discloses each limitation of the former's claims. "An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention." The '681 Patent claims a cryopreserved therapeutic composition comprising "viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult." To anticipate the '681 Patent, Koike must demonstrate that stem cells were present in umbilical cord blood. There is ample evidence in the record establishing that Koike did not demonstrate stem cells. For example, Dr. Wagner's cross examination testimony stated that Koike did not prove that there were stem cells in umbilical cord blood.[2] Wagner Tr. at 1333. Dr. Bernstein also testified that the reference does not teach stem cells nor a therapeutic composition for

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[2] Dr. Wagner's cross testimony could be further construed to support the conclusion that Koike did not cryopreserve enough cord blood, or teach cryopreservation of enough cord blood, for hematopoietic reconstitution of a human, whether adult or child, which is another limitation of the '681 Patent's claims. *See* Wagner Tr. at 1342-1343.

use in hematopoietic reconstitution. Bernstein Tr. at 2053. In this regard, the jury's verdict that the '681 patent is not anticipated by Koike is supported by substantial evidence so as to preclude judgment as a matter of law on the issue of anticipation.

The court reaches the same conclusion with respect to the '553 Patent. The '553 Patent claims in pertinent part:

> A method for hematopoietic or immune reconstitution of a human comprising:
>
> (a) isolating human neonatal or fetal blood components containing hematopoietic stem cells;
>
> (b) cryopreserving the blood components; and
>
> (c) introducing the blood components into a suitable human host.

It is undisputed that Koike did not introduce cord blood into a human, which is a necessary limitation of the '553 Patent. The defendants claim that Koike's suggestion that introducing the stem cells into a human host should be done is a sufficiently enabling disclosure to warrant a finding of anticipation. Even so, the record contains substantial evidence from which a jury could find that a person of ordinary skill in the art would not have been so enabled. For example, Dr. Wagner testified that Koike did not do a transplant, Wagner Tr. at 1333, and Dr. Bernstein testified that Koike does not introduce stem cells into a human or teach

hematopoietic reconstitution, Bernstein Tr. at 2053-2054. Again, the jury's finding that the Patents-In-Suit are not anticipated[3] is supported by substantial evidence and the court will not overturn it on this basis.

c. Indefiniteness

The defendants also argue that the '681 Patent is invalid because it is indefinite. Claim 1 of that patent covers "stem cells" "in an amount sufficient to effect hematopoietic reconstitution of a human adult. "According to the defendants, this language is indefinite as a matter of law because it is specifically drawn to an amount of stem cells, but the patent is completely silent as to a quantity. In this regard, they claim that it does not provide sufficient notice of the scope of the invention. The court is not persuaded.

Section 112 provides in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and

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[3] Given the absence of record evidence showing that Koike's compositions contained an amount of stem cells sufficient to effect hematopoietic reconstitution of a human adult, the defendants' inherent anticipation theory is an equally unpersuasive basis on which to enter judgment as a matter of law on this issue. Although recognition of an element in the prior art before the critical date is not necessary, inherent anticipation still requires that the element necessarily be present. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

> exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. The statute requires the patentee to provide the public with clear notice of what activities infringe the patent. *See Exxon Research & Eng'g Co. v. United States,* 265 F.3d 1371, 1375 (Fed. Cir. 2001); *Morton Int'l v. Cardinal Chem. Co.,* 5 F.3d 1464, 1470 (Fed. Cir. 1993). "If the claims, read in light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Shatterproof Glass Cor. v. Libbey-Woens Ford Co.,* 758 F.2d 613 624 (Fed. Cir. 1985) (citing *Georgia Pacific Corp. v. United States Plywood Corp.,* 258 F.2d 124, 136 (2d Cir. 1958)). Indefiniteness is a question of law for the court. *In re Jolly,* 172 F.2d 566, 570 (C.C.P.A. 1949); *see also Union Pacific Res. Co. v. Chesapeake Energy Corp.,* 236 F.3d 684, 692 (Fed. Cir. 2001). "In a jury trial, if there are disputed factual issues related to indefiniteness, they may be submitted to the jury for resolution." *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.,* Nos. 99-274 (SLR), 99-876 (SLR), 2004 WL 1305849, *10 (D.Del.2004) (citing *BJ Services Co. v. Halliburton Energy Serv., Inc.,* 338 F .3d 1368, 1372 (Fed. Cir. 2003)). Because a patent is presumed valid, the party asserting a defense of invalidity on the basis of claim indefiniteness bears the burden of proof by clear and convincing evidence. *See*

Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1575-76 (Fed. Cir. 1986).

It is true that the language of the '681 Patent does not specify an amount of progenitor cells nor a volume of cord blood, and the specification is silent as to a precise amount. However, these facts do not necessarily dictate that Claim 1 must fail for indefiniteness. Given that there is no determinate or determinable minimum amount of cord blood for therapeutic usefulness in humans, the record supports that the '681 Patent's claim language is as precise as the subject matter permits. Moreover, the record contains evidence establishing that a person of skill in the art would have understood what an amount of cord blood stem cells sufficient to effect hematopoietic reconstitution of a human adult means. *See Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 823 (Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986). Dr. Moore, PharmaStem's expert on hematopoiesis, testified that the Patents-In-Suit provide the reader with ample information to determine the amount of cord blood needed for transplantation in adults or children, and that the scientific community has in fact performed numerous transplants into adults. Moore Tr. at 340-348; *see also* Harris Tr. at 635-636 (for defendants' witness skilled in art stating that an amount sufficient for usefulness in a clinical setting would be "a sample that contained enough of those cells for a successful transplant"). Thus, the court can find no basis to overturn the jury's verdict that the '681 Patent is not invalid for indefiniteness.

2. The Jury's Verdict That the Defendants Contributorily Infringe the '553 Patent Cannot Stand.

The defendants claim that PharmaStem did not prove that they contributorily infringed the '553 Patent in that PharmaStem failed to adduce evidence that any of them sold or offered to sell cryopreserved cord blood to a transplanter or that cryopreserved cord blood was used by a single entity or group of entities acting in concert or working together to infringe the patent. The court agrees. Relevantly, the claim language of the '553 Patent requires:

> A method for obtaining human neonatal or fetal hematopoietic stem or progenitor cells comprising:
>
> (a) isolating human neonatal or fetal blood components containing hematopoietic stem or progenitor cells;
>
> (b) cryopreserving the blood components; and
>
> (c) thawing the blood components, such that the stem or progenitor cells are viable.

Because none of the defendants thaw or inject cord blood, both required elements of the '553 Patent's claims, there can be no literal infringement of the '553 Patent.

PharmaStem would, however, still be entitled to a finding of infringement if the jury reasonably could have found that the defendants contributorily infringed the '553 patent. *See* 35 U.S.C. § 271(c).

Section 271(c) states:

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

35 U.S.C. § 271. The verdict form required the jury to answer three questions in the affirmative in order to find that any of the defendants contributorily infringed the '553 patent. Consistent with the appropriate legal standard, the jury was required to find that (I) "cryopreserved cord blood has no substantial noninfringing use," (ii) "defendants and transplant physicians are acting in concert or working together to complete the process of infringement of claims 13, 19, 47, or 57 of the '553 patent by performing each and every one of the steps in any of those claims," and (iii) "a Defendant has contributorily infringed the '553 patent by selling or

offering to sell cryopreserved cord blood that was actually used by a third party in the direct infringement of any of claims 13, 19, 47, 53, or 57 of the '553 patent." Jury Verdict Form, Qtn. Nos. 3, 4, and 5.

PharmaStem correctly points out the existence of evidence to support the jury's affirmative answer to questions (I) and (ii) of the verdict form. The record supports a conclusion that cryopreserved cord blood is, predominantly, useful only for transplantation therapy, or the use covered by the '553 Patent. Indeed, PharmaStem adduced evidence by which a jury reasonably could have found that cord blood was viewed as medical waste prior to the inventions of the Patents-In-Suit. *See, e.g.*, Moore Tr. at 328; Broxmeyer Tr. at 365; Wagner Tr. 1195-1196.

Moreover, the jury also could have reasonably found that each of the defendants worked together with transplant physicians to complete the patented process of the asserted claims of the '553 Patent. At trial, PharmaStem adduced evidence that the defendants test the blood samples to ensure each one is sufficient for transplantation and thereby aid transplant physicians. Tr. Ex. 103; Tr. Ex. 96; Laleman Tr. at 659. The defendants marketing materials also indicate that they work with physicians in various capacities to effectuate the transplantation process. For example, CorCell's website states "CorCell and Community Blood Services (CBS) has formed a strategic partnership devoted to expertly testing, processing and storing quality cord blood stem cells for future

transplantation." Tr. Ex. 516. ViaCell's founder, Cynthia Fisher, testified that the company's mission was "to provide a niche application area between the obstetrician, the Hem/Onc and the blood banking center, as far as enabling providing cord blood stem cell banking." Fisher Tr. at 707. Cryo-Cell advertises that the units of cord blood stem cells stored at its facility are transplant-ready. Tr. Ex. 98. In addition, PharmaStem presented evidence that each of the defendants has at least one representative who liaises in some capacity with transplant physicians, i.e., Dr. Goldberg of CorCell and Dr. O'Neil of Cryo-Cell. CBR designates a Director of the Facility to oversee procedures regarding the release of cord blood units for transplantation. Tr. Ex. 110. Viacell seeks advice and counsel on nucleated cell counts and volumes useful for transplantation from its Medical Scientific Advisory Board, on which five of the seven members are prominent transplant doctors or physicians with extensive experience in hematology, oncology, and/or transfusion medicine. Tr. Ex. 253, Tr. at 1461-63; *see also* Wagner Tr. at 1389. Finally, there is also evidence in the record showing that each of the defendants maintain records and/or other materials regarding its cord blood units which it releases to physicians to assist the transplantation process. CorCell maintains records on the cord blood units it releases, Tr. Ex. 274, and requests feedback from the transplant facility as part of its standard operating procedures, Tr. Ex. 215. Cryo-Cell provides directions to transplant physicians on how to thaw the cryopreserved cord blood unit it provides. Tr. Ex. 97. CBR has a similar document setting forth the detailed protocol between CBR and the transplant

physician when a cord blood unit is requested and released. Tr. Ex. 110. In view of this evidence, it was not unreasonable for the jury to have found that the defendants and transplant physicians worked together to infringe the '553 patent.

Nevertheless, with respect to the third question on the verdict form, there is simply no evidence in the record to support the jury's affirmative answer. It is undisputed that the defendants do not own the cord blood units. Rather the units are owned by the clients, or families, and the defendants in turn provide services with respect to the processing and storing of the compositions. Although the defendants charge enrollment, processing, and banking fees with respect to their storage services, they do not *sell* or *offer to sell* the cord blood units. Indeed, the record evidence on this issue is clear that the defendants sell a service, not cord blood units. *See* Hendrix Tr. 1042; Tr. 2653; Wagner Tr. 1278.

Tellingly, PharmaStem cannot direct the court to a single fact in evidence that would support a finding that any of the defendants sell or offer to sell cord blood. PharmaStem attempts to overcome this deficiency in the record by arguing that Section 271(c) focuses on the financial benefit derived by the seller regardless of the source. But the statute could not be clearer. Section 271(c) liability is clearly dependant upon the accused infringer's selling or offering to sell a component of the patented process, here cord blood units. *See* 35 U.S.C. § 271(c). Drawing all reasonable inferences from the evidence in favor of PharmaStem, the court agrees with the

defendants that the jury's finding on the element of contributory infringement is not supported by substantial evidence. In this regard, the jury's verdict on contributory infringement cannot stand. The court finds as matter of law that the defendants' services do not infringe the '553 patent.[4]

B. Defendants' Motion for a New Trial

The defendants alternatively contend that the court should set aside the judgment and grant a new trial because the jury's verdict was against the great weight of the evidence. The court agrees with respect to the jury's finding that the 100% of the defendants' cord blood units infringe the '681 patent and accordingly will grant a partial new trial on this issue.

1. Inventorship

The defendants first claim that a new trial is warranted because the great weight of the evidence established that the Patents-In-Suit are invalid for failure to name one of the inventors, Dr. Pablo Rubinstein. The court does not agree.

Every patent receives the presumption that its inventors are the true and only inventors. *See e.g., Acromed Corp. v. Sofamor Danek Grp., Inc.*, 253 F.3d 1371, 1379 (Fed. Cir. 2001). Invalidity for failure to name an inventor must be established by clear and convincing evidence. *See id.* at 1379. To be a joint

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[4] Because the court finds that the defendants do not infringe the '553 Patent, it will not address the issue of willful infringement with respect to that patent.

inventor, one must "contribute in some significant manner to the conception of the invention." *Fina Oil & Chem. Co. v. Ewen,* 123 F.3d 1466, 1473 (Fed. Cir. 1997). Specifically, each person claiming to be an inventor must have contributed to the conception of the invention. *Acromed,* 253 F.3d at 1379. Beyond conception, the purported inventor must demonstrate that he made "a contribution to the claimed invention that is not insignificant in quality, when contribution is measured against the dimension of the full invention, and [did] more than merely explain to the real inventors well-known concepts and/or the current state of the art." *Id.* at 1379.

Although the defendants point to evidence from which a jury could have found Dr. Rubinstein's contributions to be significant, PharmaStem adduced at least an equal amount of evidence that his contribution did not rise to the level of inventorship. Indeed, a jury could conclude from the record that Dr. Rubinstein provided consultation on cryo-preservation methods which were already available in the art. *See* Bernstein Tr. at 1176-1177. Moreover, Dr. Rubinstein admitted that he published his cryopreservation techniques more than one year prior to the inventions of the Patents-In-Suit, Rubinstein Tr. at 1176-1177, which would allow a jury to conclude that any contribution he made was rendered prior art by the time of the patenting of the invention. *See* 35 U.S.C. § 102; *Hess v. Advanced Cardiovascular Syss.*, 106 F.3d 976, 981 (Fed. Cir. 197). In light of these significant pieces of evidence supporting the jury's finding that Dr. Rubinstein was not improperly omitted as an inventor, the court

finds no basis to grant a new trial on the issue of invalidity for failure to name an inventor.

2. Inequitable Conduct

The defendants also argue that the jury's finding that PharmaStem did not engage in inequitable conduct before the PTO in the procurement of the '681 and '553 Patents is against the great weight of the evidence. The court, however, is not persuaded that the jury's finding on this issue warrants a new trial. The burden is on the party seeking to invalidate the patents to prove inequitable conduct by clear and convincing evidence. In view of the defendants' burden, the jury's verdict was not against the great weight of the evidence.

As evidence of PharmaStem's alleged inequitable conduct, the defendants point to the PharmaStem's failure to disclose two pieces of information to the PTO. First, after PharmaStem had presented its arguments to the PTO in reexamination, but several months before the '681 Patent reissued, the European Patent Office ("EPO") denied PharmaStem's European counterpart application, rejecting its argument that Koike does not teach stem cells. PharmaStem did not bring the EPO's rejection of its argument to the attention of the PTO before reissue. Second, in its opinion, the EPO cites the 1997 Broxmeyer article for the proposition that relevant scientific community considered progenitor cell assays to be reliable assays for stem cells. In view of these facts, the defendants argue that the jury's finding that PharmaStem did not engage in inequitable conduct

before the PTO is against the great weight of the evidence.

"One who alleges inequitable conduct arising from a failure to disclose prior art must offer clear and convincing proof of the materiality of the prior art, knowledge chargeable to the applicant of that prior art and of its materiality, and the applicant's failure to disclose the prior art, coupled with an intent to mislead the PTO." *Molins,* 48 F.3d at 1178; *accord Rockwell Techs., LLC v. Spectra Physics Lasers, Inc.,* 2002 WL 531555, at *3 (D. Del. Mar. 26, 2002). "Materiality and intent to deceive are distinct factual inquiries, and each must be shown by clear and convincing evidence." *Life Techs., Inc. v. Clontech Labs., Inc.,* 224 F.3d 1320, 1324 (Fed. Cir. 2000); *accord Isco Int'l, Inc. v. Conductus, Inc.,* 2003 WL 22006253, at *6 (D. Del. Aug. 21, 2003). Patent applicants have a duty to disclose to the PTO "any material prior art or other information cited or brought to their attention in any related foreign application." Manual of Patent Examining Procedure § 2001.06(a) (4th ed., rev. 8, Oct. 1981). However, a finding of inequitable conduct for nondisclosure of information requires proof that the applicant made a deliberate decision to withhold a known material reference from the PTO. *See Molins PLC v. Textron, Inc.,* 48 F.3d 1172, 1181 (Fed. Cir. 1995).

Given the controlling standards, PharmaStem adduced significant evidence to rebut the defendants' inequitable conduct case. Specifically, the EPO's decision applied European, as opposed to United States, patent laws, and examined different claims than the ones at issue before the PTO in the

reexamination. Tr. Ex. 1013. Moreover, there is no dispute that PharmaStem disclosed Koike to the PTO in the reexamination, and that the PTO came to its own conclusion as to what the reference taught. With respect to the Broxmeyer article, it was published nearly ten years after the initial filing of the Patents-In-Suit, and therefore not a prior art reference. Tr. Ex. 1015. Further lending credence to PharmaStem's view that the article was not material, the EPO characterized the Broxmeyer article as "indirect evidence" and cited it in the portion of the opinion on novelty, which was not at issue in the reexamination before the PTO. Tr. Ex. 1013. When viewed as a whole, the record more than supports a conclusion that PharmaStem did not possess the requisite intent to deceive the PTO and therefore did not engage in inequitable conduct.

3. Infringement of the '681 Patent

a. D. Hendrix's Testimony

As one of the bases for their motion for a new trial on infringement of the '681 Patent, the defendants contend that Dr. Mary Hendrix, PharmaStem's infringement expert, should not have been permitted to testify. During the pretrial stage of proceedings, the defendants objected to Dr. Hendrix's testimony in a motion *in limine* and then again at the close of trial moved to strike the doctor's testimony. The court denied both of these motions, but will revisit its rulings in light of the evidentiary record now before it.

Rule 702 has three requirements as to expert opinions: 1) the witness must be an expert; (2) the witness must testify to scientific, technical, or other specialized knowledge; and 3) the testimony must assist the trier of fact. *See United States v. Velasquez,* 64 F.3d 844, 849 (3d Cir. 1995) (citations omitted). The U.S. Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579 (1993), established a gatekeeping role for trial court judges in determining the admissibility of expert testimony on scientific evidence. When an expert bases opinion testimony on scientific knowledge, the testimony will not be admitted unless it is derived by the scientific method and is supported by "appropriate validation." *Daubert,* at 590. This standard of evidentiary reliability focuses on the scientific validity of the expert's methods rather than the soundness of his specific conclusions. *Id. at 589* ("[the] inquiry into the reliability of scientific evidence .... requires a determination as to its scientific validity."); *see also Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir. 2000); *United States v. Shea,* 957 F. Supp. at 337. An expert's opinion is reliable if it is based on the "methods and procedures of science" rather than on "subjective belief or unsupported speculation"; the expert must have "good grounds" for his or her belief. *See Daubert,* 509 U.S. at 589.

The defendants contend that the subject of Dr. Hendrix's testimony was not one for which expertise was necessary in that she based her infringement opinion entirely on an analysis of the defendants' marketing materials, without ever considering any data regarding the composition of the defendants'

cord blood units. Dr. Hendrix is an accomplished stem cell biologist, but is not qualified as an expert in marketing or advertising. Moreover, her so-called analysis of the defendants' marketing materials was well within the jury's common knowledge, common sense and common experience. *See United States v. Stevens,* 935 F.2d 1380, 1399-1400 (3d Cir. 1991) (upholding Federal Rule of Evidence 403 exclusion of expert testimony regarding eye witness identification where the evidence was susceptible of elucidation without specialized knowledge and jury could have ascertained through common sense). In view of these considerations, the court is persuaded that Dr. Hendrix's conclusion, evidenced in her expert report and adduced through her testimony, that 100% of the defendants' cord blood units infringe the '681 Patent was based upon a legally improper methodology that was unreliable as a matter of law under *Daubert.*

Significantly, Dr. Hendrix's admitted that she did not review or analyze any of the defendants' cord blood samples in reaching her opinion. Hendrix Tr. at 1038. Moreover, she explicitly testified that her opinion that all of the defendants' cord blood units infringe the '681 Patent was based on the fact that the defendants "promise stem cells for pediatric and adult transplantation." Hendrix Tr. at 1021. In this regard, her opinions are not based upon any methods or procedures of science in general and certainly not upon her specific expertise as a stem cell biologist, no matter how knowledgeable she may have been in that field. The court therefore determines that her opinion of infringement is no more than a lay-person's interpretation of the defendants' marketing materials. The materials relied upon by Dr. Hendrix

may be persuasive on the issue of infringement, but permitting PharmaStem to couch its presentation of this evidence in the form of an expert opinion was an error.

b. The Lack of Record Evidence that 100% of the Defendants' Units Infringe the '681 Patent

Claim 1 of the '681 Patent covers compositions containing stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult." To prove infringement, therefore, PharmaStem was required to adduce evidence that the defendants cord blood units contained an amount of stem cells sufficient for transplantation into an adult. In the absence of Dr. Hendrix's testimony, the record is void of any proof to support a finding that 100% of the defendants' cord blood units infringe the '681 Patent. To the contrary, the record overwhelmingly indicates that cord blood units will *not all* contain sufficient cells to reconstitute an adult. *See* Wagner Tr. at 1270; *see also* Tr. Ex. 1370 at 30 (PharmaStem telling the PTO that cord blood units "are highly variable in their stem cell content such that any particular cord blood collection may have low or no stem cells"). The jury's finding that *all* of the defendants' cord blood units infringe the '681 Patent, consequently, was against the great weight of the evidence.

At the same time, however, the record suggests that at least some of the defendants' cord blood units infringe in that there is evidence of successful transplants of the defendants'

compositions into human adults. *See, e.g.*, Tr. Ex 115 (circumstantial evidence in the form of statements on CBR's website that a "newborn's cord blood stem cells were transplanted to her mother to treat chronic myelogenous leukemia," and that other transplants have occurred for the newborn's mother father and cousin); Tr. Ex. 103 (draft of ViaCord's private placement memorandum acknowledging that adult transplants have occurred). As a result, the court will grant a new trial, excluding Dr. Hendrix's expert testimony, on the issue of infringement of the '681 Patent and the resultant damages therefrom.[5]

IV. CONCLUSION

For the aforementioned reasons, the court will enter judgment as a matter of law that the defendants do not infringe the '553 Patent and grant a new trial on the issue of infringement and damages with respect to the '681 Patent. In all other aspects, the motions filed by the parties are denied. An order to this effect will accompany this opinion.

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[5] Again, in light of its granting a new trial on the infringement issue, the court will not rule on the issue of willful infringement with respect to the '681 Patent.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PHARMASTEM THERAPEUTICS, INC. Plaintiff, v. VIACELL INC., et al., Defendants.	C.A. No. 02-148-GMS

ORDER

For the reasons set forth in the court's memorandum opinion issued contemporaneously herewith, IT IS HEREBY ORDERED that:

1. Joint Renewed Motion by ViaCell, Inc, Cyro-Cell, Inc, CorCell, Inc, CBR Systems, Inc. for Judgment as a Matter of Law or in the Alternative, for a New Trial (or for Remittitur) (D.I. 448) is GRANTED IN PART.

2. PharmaStem, Inc.'s Motion for Enhanced Damages, Attorneys' Fees, Pre-Judgment Interest and Post Judgment Interest (D.I. 446) is DENIED.

3. PharmaStem, Inc.'s Motion for a Permanent Injunction (D.I. 447) is DENIED.

4. PharmaStem's Motion to Strike the Affidavit of Chris Adams (D .I. 487) is DENIED as moot.

5. The clerk shall enter judgment in favor of the defendants and against the plaintiff on the claim of infringement of U.S. Patent No. 5,192,553.

6. A new trial shall be held on the issue of infringement and damages with respect to U.S. Patent No. 5,004,681.

Dated: September 15, 2004

s/

UNITED STATES DISTRICT JUDGE

Filed
Sep 15 2004
U.S. District Court
District of Delaware

APPENDIX C

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

PHARMASTEM THERAPEUTICS, INC. Plaintiff, v. VIACELL INC., et al., Defendants.	C.A. No. 02-148-GMS

MEMORANDUM

I. INTRODUCTION

On February 22, 2002, PharmaStem Therapeutics, Inc. ("PharmaStem") filed this lawsuit against ViaCell, Inc. ("ViaCell"), Cryo-Cell International, Inc. ("Cryo-Cell"), CorCell, Inc. ("CorCell"), StemCyte, Inc. ("StemCyte"), CBR Systems, Inc. ("CBR"), Birthcells Technology, Inc. ("Birthcells"), Nustem Technologies, Inc. ("Nustem"), and Bio-Cell, Inc. ("Bio-Cell") (collectively, the "defendants"),[1] alleging infringement of United

[1] A default judgment was subsequently rendered against NuStem on July 10, 2002. StemCyte and PharmaStem entered a settlement agreement before trial, and StemCyte accordingly was dismissed from this action on October 21, 2003.

States Patents Nos. B1 5,004,681 ("'681 Patent") and 5,192,553 ("'553 Patent"). On October 29, 2003, the jury returned a unanimous verdict on all claims in favor of Pharmastem. The parties then filed several post-trial motions.[2] On September 15, 2004, the court issued a Memorandum Opinion and Order (the "Post-trial Order") addressing the post-trial motions. The court concluded that the defendants do not infringe the '553 patent and granted a partial new trial on the issue of infringement and damages with respect to the '681 Patent.[3]

Following the Post-trial Order, CorCell and Cryo-Cell filed a motion for partial reconsideration of the court's post-trial rulings. CBR and Viacell joined the motion and submitted individual memoranda that addressed issues specific to each of them. In addition, ViaCell filed a motion for entry of separate and final judgment pursuant to Federal Rule of Civil Procedure 54(b) and a motion for certification for

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[2] ViaCell filed a renewed motion for judgment as a matter of law, and, in the alternative, a motion for a new trial or for a remittitur, in which the defendants CBR, CorCell, and Cryo-Cell joined. ViaCell filed another alternative motion, in which the other defendants also joined, for findings by the court and/or to alter or amend judgment pursuant to Federal Rule of Civil Procedure 52, 59(e) and/or the court's equitable power. PharmaStem filed a motion for enhanced damages, attorneys' fees, pre-judgment interest and post judgment interest, a motion for a permanent injunction, and a motion to strike the affidavit of Chris Adams submitted in support of ViaCell's motion to alter or amend the judgment.

[3] For a complete recitation of the facts, procedural history, and post-trial rulings of this case, please see *Pharmastem Therapeutics, Inc. V. Viacell, Inc.*, C.A. No. 02-148 GMS, 2004 WL 2127192 (D. Del. Sept. 15, 2004).

interlocutory appeal pursuant to 28 U.S.C. § 1292(b), in which CBR, CorCell, and Cryo-Cell joined. PharmaStem filed a motion for a preliminary injunction, as well as a motion for entry of separate and final judgment pursuant to Federal Rule of Civil Procedure 54(b). For the following reasons, the court will grant the defendants' motion for partial reconsideration, reverse its post-trial ruling as to the '681 patent, and enter judgment as a matter of law ("JMOL") that the defendants do not infringe the '681 patent.[4]

II. STANDARDS OF REVIEW

A. Motion For Reconsideration

As a general rule, motions for reconsideration should be granted only "sparingly." *Tristrata Tech., Inc. v. ICN Pharms., Inc.*, 313 F. Supp. 2d 405, 407 (D. Del. 2004); *Karr v. Castle*, 768 F. Supp. 1087, 1090 (D. Del. 1991). In this district, these types of motions are granted only if it appears that the court has patently misunderstood a party, has made a decision outside the adversarial issues presented by the parties, or has made an error not of reasoning, but of apprehension. *See, e.g., Shering Corp. v. Amgen, Inc.*, 25 F. Supp. 2d 293, 295 (D. Del. 1998); *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239,

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[4] The court will deny the plaintiff's and the defendants' motions for entry of separate and final judgment pursuant to Federal Rule of Civil Procedure 54(b), the defendants' motion for certification for interlocutory appeal pursuant to 28 U.S.C. § 1292(b), and the plaintiff's motion for preliminary injunction, because the court's ruling on the motion for reconsideration renders them moot.

1240 (D. Del.1990) (citing *Above the Belt, Inc. v. Mel Bonhannan Roofing, Inc.*, 99 F.R.D. 99 (E.D. Va. 1983)); *see also Karr*, 768 F. Supp. at 1090 (citing same). Moreover, even if the court has committed one of these errors, there is no need to grant a motion for reconsideration if it would not alter the court's initial decision. *See Pirelli Cable Corp. v. Ciena Corp.*, 988 F. Supp. 424, 455 (D. Del. 1998). Finally, motions for reconsideration "should not be used to rehash arguments already briefed." *TI Group Automotive Systems, (North America), Inc. v. VDO North America L.L.C.*, 2002 U.S. Dist. LEXIS 1018, 2002 WL 87472 (D. Del. 2002) (citation omitted); *see also Quaker Alloy Casting v. Gulfco Industries, Inc.*, 123 F.R.D. 282, 288 (N.D. Ill. 1988) ("This Court's opinions are not intended as mere first drafts, subject to revision and reconsideration at a litigant's pleasure.").

B. Renewed Motion for Judgment as a Matter of Law

Pursuant to Federal Rule of Civil Procedure 50, a court may render JMOL after the moving party is fully heard on an issue at trial, if "there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." *Walter v. Holiday Inns, Inc.*, 985 F.2d 1232, 1238 (3d Cir. 1993) (citation omitted). If the court denies a motion for JMOL during trial, the motion may be renewed within ten days of entry of judgment in the case. FED. R. CIV. P. 50(b). To prevail on a renewed motion for JMOL following a jury trial, a party "'must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were,

that the legal conclusion(s) implied [by] the jury's verdict cannot in law be supported by those findings.'" *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1348 (Fed. Cir. 1998) (quoting *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893 (Fed. Cir. 1984)). "'Substantial' evidence is such relevant evidence from the record taken as a whole as might be accepted by a reasonable mind as adequate to support the finding under review." *Perkin-Elmer Corp.*, 732 F.2d. at 893. In assessing the sufficiency of the evidence, the court must draw all reasonable inferences from the evidence in the light most favorable to the nonmovant. *Id.; Richardson-Vicks Inc. v. UpJohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The appropriate inquiry is whether a reasonable jury, given the facts before it, could have arrived at the conclusion it did. *Dawn Equip. Co. v. Kentucky Farms, Inc.*, 140 F.3d 1009, 1014 (Fed. Cir. 1998). The court may not determine the credibility of the witnesses nor "substitute its choice for that of the jury between conflicting elements of the evidence." *Perkin-Elmer Corp.*, 732 F.2d at 893.

III. DISCUSSION

In the Post-trial Order, dated September 15, 2004, the court denied the defendants' motion for JMOL on the issue of infringement and damages with respect to the '681 patent, but granted the defendants' motion in the alternative for a new trial on this issue. By their motion, the defendants request the court to reconsider its Post-trial Order and grant the motion for JMOL.

The defendants contend that Pharmastem failed to meet its burden with respect to

infringement of the '681 patent because: (1) the issue before the jury, as Pharmastem chose to try the case, was whether all of the cord blood units processed and cryopreserved by the defendants infringe the '681 patent, and they do not; and (2) Pharmastem was obligated, as a matter of law, to adduce evidence with respect to specific units of cord blood stored by the defendants and to show with respect to those specific units that they contain sufficient stem cells to reconstitute a human adult, and did not meet this obligation. The defendants rely on the Post-trial order for support.

In response, Pharmastem asserts that it adduced substantial evidence at trial that the defendants infringe the '681 patent. Pharmastem also asserts that the scientific and medical evidence support cord blood transplantation in adults, and that the defendants use that evidence to promote their cord blood banking services for adult use. Pharmastem supports its assertions with statements from the defendants' marketing materials regarding the potential for adult transplantation. Pharmastem also relies on the defendants' testimony regarding their marketing materials, the threshold quantity of cord blood they collect, and the threshold amount of cells they require. Lastly, Pharmastem relies on the Post-trial Order, which states, "[t]he record suggests that at least some of the defendants' cord blood units infringe in that there is evidence of successful transplants of the defendants' compositions into human adults." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, C.A. No. 02-148 GMS, 2004 WL 2127192, at *11 (D. Del. Sept. 15, 2004).

The parties agree that the only disputed issue at trial was which of the defendants' cord blood units contain stem cells in an amount sufficient to effect hematopoietic reconstitution of an adult. According to Pharmastem's presentation to the jury, the answer to that issue was 100%. In other words, Pharmastem's position at trial was that "all" of the defendants' cord blood units infringe the '681 patent.[5] Pharmastem's post-trial motions, as well as its motion for preliminary injunction are unclear as to whether it has changed its position regarding infringement. For example, Pharmastem's opposition to CBR's motion for judgment as a matter of law states that "CBR's admissions in its marketing documents, the standard operating procedures of the company, as well as the testimony of Dr. Harris support a finding that all of the samples infringe...." (D.I. 418, at 3). In addition, Pharmastem's opening brief in support of its motion for preliminary injunction defines the issue as follows: "As the Court recognizes, the dispute is not whether any of the defendants' cord blood units infringe, as 'the record suggests that at least some of the defendants' cord blood units infringe ...', but whether *all (i.e., every*

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[5] Indeed, when referring to question fourteen of the verdict form during closing arguments (*i.e.* the question that directed the jury to enter the number of cord blood units that infringe the '681 patent), counsel for Pharmastem told the jury to base the number of units that infringe on the numbers provided by the defendants-that is, 34,293 for ViaCell; 49,646 for Cryo-Cell; 4,640 for CorCell; and 34,649 for CBR. These numbers are equivalent to the total number of cord blood units stored by each of the defendants. Further, Pharmastem did not refer to any specific unit or units in presenting its case to the jury. Rather, Pharmastem referred to the defendants' cord blood units as a whole.

single one) of the defendants' cord blood units infringe." (D.I. 559, at 5) (emphasis added). Pharmastem's opposition brief to the motion for reconsideration, however, states that "[t]here is abundant medical, scientific, and party proof that the vast majority, if not all, of the defendants cord blood units contain stem cells in an amount sufficient to effect hematopoietic reconstitution of an adult." (D.I. 571, at 14). After reviewing the record, the post-trial motions, and the motion for reconsideration, the court concludes that Pharmastem's position, prior to its briefing on the motion for reconsideration, was that 100% of the defendants cord blood units infringe the '681 patent.[6] Therefore, in order to meet its burden, Pharmastem had to adduce evidence that 100% of the defendants' cord blood units contained stem cells in a sufficient amount to reconstitute a human adult. Pharmastem, however, did not meet its burden.

First, the court has already determined that "the record overwhelmingly indicates that cord blood units will not all contain sufficient cells to reconstitute an adult." *Pharmastem Therapeutics, Inc. V. Viacell, Inc., Et Al.*, No. C.A. 02-148 GMS, 2004 WL 2127192, at *11 (D. Del. Sept. 15, 2004). For example, the '681 patent illustrates that each cord blood sample will vary in terms of its cell count. '681 patent Table III (providing cord blood samples with different total volumes and total nucleated blood cells). In addition, Pharmastem represented to

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[6] The court will hold Pharmastem to its presentation to the jury, as well as its assertions in its post-trial motions and its motion for preliminary injunction.

the PTO that cord blood units "are highly variable in their stem cell content such that any particular cord blood collection may have low or no stem cells." Tr. Ex. 1370, at 30; *see* Wagner Tr. at 1270. The court, therefore, will affirm its post-trial conclusion that "[t]he jury's finding that *all* of the defendants' cord blood units infringe the '681 patent... was against the great weight of the evidence." *Pharmastem*, 2004 WL 2127192, at *11.

Second, even assuming that "at least some of the defendants' cord blood units infringe in that there is evidence of successful transplants of the defendants' compositions into human adults," the court finds that Pharmastem presented no evidence to the jury from which it could conclude that any specific cord blood unit or units stored by any of the defendants contained stem cells in a sufficient amount to reconstitute a human adult. All of the defendants made available to Pharmastem their data with respect to individual units. Pharmastem, however, did not have its infringement expert, Dr. Mary Hendrix ("Dr. Hendrix"), testify regarding whether the data indicated that any of the defendants' units infringed. In fact, Dr. Hendrix testified that she did not review the defendants' data. Hendrix Tr. at 1038. Rather, Dr. Hendrix based her infringement opinion on the fact that the defendants "promise stem cells for pediatric and adult transplantation." *Pharmastem*, 2004 WL 2127192, at *11.

In addition, Pharmastem presented no evidence to the court regarding how to quantify the defendants' infringement and damages flowing from

the infringement. Instead, Pharmastem chose to offer the evidence of successful adult transplants to prove that 100% of the defendants' units infringe. However, evidence of one successful adult transplant with a single cord blood unit does not prove that any other unit has sufficient stem cells to reconstitute a human adult because, as previously stated, cord blood units are highly variable in their stem cell content. As such, the court will not infer that 100% of the defendants' units infringe based on the defendants' statements regarding adult transplantation. Pharmastem failed to present evidence to the jury from which it could conclude that any specific cord blood unit or units stored by any of the defendants contained stem cells in a sufficient amount to reconstitute a human adult. The court, therefore, cannot determine which or how many of the defendants' units infringe, or how to quantify damages for infringement. Thus, the defendants are entitled to JMOL because there was no legally sufficient evidentiary basis for a reasonable jury to find that all, or any specific number, of the defendants cord blood units infringe the '681 patent.

Dated December 14, 2004 s/
UNITED STATES
DISTRICT JUDGE

FILED
DEC 14 2004
U.S. DISTRICT COURT
DISTRICT OF DELAWARE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PHARMASTEM THERAPEUTICS, INC. Plaintiff, v. VIACELL INC., et al., Defendants.	C.A. No. 02-148-GMS

ORDER

For the reasons set forth in the court's Memorandum issued contemporaneously herewith, IT IS HEREBY ORDERED that:

1. The Motion by ViaCell, Inc., Cryo-Cell, Inc., CorCell, Inc., CBR Systems, Inc. for Partial Reconsideration of the Court's Post-Trial Rulings (D.I. 547, 551, 552) is GRANTED.

2. PharmaStem, Inc.'s Motion for a Preliminary Injunction (D.I. 558) is DENIED as moot.

3. The Motion by ViaCell, Inc., Cryo-Cell, Inc., CorCell, Inc., CBR Systems, Inc. for Entry of Separate and Final Judgment

Pursuant to Federal Rule of Civil Procedure 54(b) (D.I. 547, 548, 552) is DENIED as moot.

4. The Motion by ViaCell, Inc., Cryo-Cell, Inc., CorCell, Inc., CBR Systems, Inc. for Certification for Interlocutory Appeal Pursuant to 28 U.S.C. § 1292(b) (D.I. 547, 549, 552) is DENIED as moot.

5. Pharmastem, Inc.'s Motion for Entry of Final Judgment Pursuant to Federal Rule of Civil Procedure 54(b) (D.I. 563) is DENIED as moot.

6. The clerk shall enter judgment in favor of the defendants and against the plaintiff on the claim of infringement of U.S. Patent No. B1 5,004,681.

Dated: December 14, 2004 s/
UNITED STATES
DISTRICT JUDGE

FILED
DEC 14 2004
U.S. DISTRICT COURT
DISTRICT OF DELAWARE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PHARMASTEM THERAPEUTICS, INC. Plaintiff, v. VIACELL INC., et al., Defendants.	C.A. No. 02-148-GMS

JUDGMENT IN A CIVIL CASE

For the reasons stated in the Court's Opinion issued on December 14, 2004;

IT IS HEREBY ORDERED AND ADJUDGED that judgment be and is hereby entered in favor of the Defendants, Viacell Inc., et al AND against the Plaintiff, Pharmastem Therapeutics, Inc. on the claim of infringement of U.S. Patent No. B15,004,681.

Dated: December 14, 2004 s/
April Walker
(By) Deputy Clerk

FILED
DEC 14 2004
U.S. DISTRICT COURT
DISTRICT OF DELAWARE

APPENDIX D

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

05-1490, -1551

PHARMASTEM THERAPEUTICS, INC.
Plaintiff-Appellant,

v.

VIACELL, INC.,
Defendant-Cross Appellant,

and

CRYO-CELL INTERNATIONAL, INC., CORCELL, INC.,
Defendant-Cross Appellants,

and

CBR SYSTEMS, INC. (formerly known as Cord Blood Registry, Inc.),
Defendant-Cross Appellant,

and

BIRTHCELLS TECHNOLOGY, INC. and BIO-CELL, INC.,
Defendants.

ORDER

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellant, and the petition for rehearing, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on September 11, 2007.

FOR THE COURT,

s/

Jan Horbaly
Clerk

FILED
U.S. COURT OF APPEALS
FOR
THE FEDERAL CIRCUIT

SEP 4 - 2007

JAN HORBALY
CLERK

Dated: 09104/2007

cc: Paul Andre
Paul Ware, Jr., James Rodgers
William Abrams

PHARMASTEM THERAPEUTICS V VIACELL,
2005-1490, - 1551
(DCT - 02-CV-148)

APPENDIX E

Washington, D.C. 20231

CONTROL NUMBER	FILING DATE	PATENT UNDER REEXAMINATION	ATTORNEY DOCKET NO.
90/003, 182	8/30/93	5004681	

HM32 / 0111

EXAMINER	
WITZ, J	
ART UNIT	PAPER NUMBER
1651	

LESLIE MISROCK
PENNIE & EDMONDS
1155 AVENUE OF
THE AMERICAS
NEW YORK NY 10036

DATE MAILED 01/11/00

NOTICE OF INTENT TO ISSUE REEXAMINATION CERTIFICATE

1. ☒ Examination has been terminated in this reexam proceeding and a Certificate will be issued in due course in view of:

   a. ☒ Patent owner's communication filed on: 4-26-99

   b. ☐ Patent owner's late response filed on: _____

   c. ☐ Patent owner's failure to file an appropriate response to the Office action dated: _____

d. ☐ Patent owner's failure to timely file an Appeal Brief. 37 C.F.R.1.192.

e. ☐ Other: _____

The Reexamination Certificate will indicate the following:

f. Change in the Specification: ☐Yes, ☒No

g. Change in the Drawings: ☐Yes, ☒No

h. Status of the Claims:

(1) Patent claim(s) confirmed: 5

(2) Patent claim(s) amended: 1–4

(3) Patent claim(s) cancelled: 6–9

(4) New claim(s) patentable: _____

2. ☒ Note attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submissions should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation."

3. ☐ Note attached NOTICE OF REFERENCES CITED, PTO - 892, which is a part of this communication. The listed references are considered pertinent to the claimed invention,

but the claims are deemed to be patentable thereover.

4. ☒ Note attached LIST OF REFERENCES CITED, PTO - 1449, which is part of this communication and serves as an acknowledgment of receipt of patent owner's prior art statement. The references which were considered have been initialed on the form by the examiner and the claims are deemed patentable thereover.

5. ☐ The drawing correction request filled on_____: ☐is, ☐is not, approved.

6. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has:

☐been received ☐ not been received,

☐been filed in Serial No._____

filed on_____

7. ☐ Note Examiner's Amendment (attachment).

8. ☐ Other (attachment).

cc: Requester

Reexamination

STATEMENT OF REASONS FOR PATENTABILITY AND/OR CONFIRMATION

The following is an examiner's statement of reasons for patentability and/or confirmation of the claims found patentable in this reexamination proceeding:

The amendment filed on July 9, 1999 in response to the Office Action mailed March 1, 1999 canceled claims 6-12 and amended claim 1 to read:

1. A cryopreserved therapeutic composition comprising:

viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells.

The claims now require that the composition is both "cryopreserved" and "therapeutic". The term "cryopreserved" now requires that the composition is in the state or cryopreservation or has been cryopreserved. The claims also still require the presence of an amount of cryopreservative sufficient for cryopreservation of the cells contained in the composition. The term "therapeutic" requires the composition be suitable for therapy of an individual. Further, the composition now requires the presence

of an amount of viable human neonatal or fetal hematopoietic stem cells sufficient to effect hematopoietic reconstitution of a human adult and that this amount of viable human neonatal or fetal hematopoietic stem cells has been derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human.

The claims as amended now avoid the prior art for the following reasons. First, it was noted that the only piece of prior art which taught a composition which could have contained an amount of viable human neonatal or fetal hematopoietic stem cells sufficient to effect hematopoietic reconstitution of a human adult was the reference of Ende. The Ende reference, published in 1972, recited the treatment of an individual undergoing treatment for leukemia who received a series of cord blood infusions from multiple donors and showed a transient change in red blood cell phenotype. Even though the authors of the Ende article describe the procedure as "transplantation", it is clear that such treatment did not result in hematopoietic reconstitution. Further, since no HLA typing was performed, and multiple infusions were performed, one of ordinary skill in the art would have taken the disclosure of Ende to be equivalent to blood transfusions and would have had no expectation that the hematopoietic reconstitution of a human adult could have been performed. As a transfusion composition, one of ordinary skill would have had no motivation to cryopreserve the cord blood, since whole blood for transfusion is not frozen, but stored at 4°C and Ende further points out that any hospital with a maternity ward would provide sufficient aliquots of fresh cord blood.

The remaining references that recited umbilical cord blood, specifically the Koike and Vidal references, recited the cryopreservation of a Ficoll-Hypaque fraction of umbilical cord blood and did not provide any evidence that viable human neonatal or fetal hematopoietic stem cells were present in the thawed samples. Per the Bernstein Declaration, since hematopoietic stem cells cannot be identified visually, the only way to determine the presence of viable human neonatal or fetal hematopoietic stem cells was a direct functional test of injecting the cells into an individual devoid of hematopoietic stem cells and observe if hematopoietic reconstitution occurred. Since hematopoietic stem cells engage in both replication and differentiation, the presence of progenitors (differentiated stem cells) is not predictive of the presence of stem cells. All of the prior art references which taught the cryopreservation of a Ficoll-Hypaque fraction of umbilical cord blood assayed for the presence of progenitor cells and merely theorized on the presence of stem cells. None of the prior art references demonstrated the presence of stem cells in the umbilical cord blood. This disclosure combined with the acknowledged sensitivity of hematopoietic stems cells from fetal liver and thymus to cryopreservation and the fact that DMSO is toxic to fetal liver progenitor cells at concentrations nontoxic to bone marrow cells provides an unpredictability in the art of cryopreservation of stem cells from different sources that renders the suggestions of the prior art references as to the therapeutic uses of umbilical cord blood (whether cryopreserved or not) as a source of hematopoietic stems cells a situation of "obvious to

try", which fails to provide a prima facie finding of obviousness.

The references presented in the Information Disclosure Statement filed April 26, 1999, are drawn to the presence of hematopoietic stems cells in peripheral blood (Barr reference) and the presence of stem cells as measured by CFUs in fetal blood (Fliedner reference), but neither reference addresses the presence of hematopoietic stem cells in umbilical cord or placental blood, that these cells may successfully be cryopreserved, or that, as a collection from a single human at birth, these cells may comprise an amount that is sufficient to effect hematopoietic reconstitution of a human adult.

Therefore, in view of the amendments to the claims and in view of the arguments and evidence provided by Patent Owners in the Response filed April 26, 1999, the claims of record are deemed patentable over the prior art.

Any comments considered necessary by PATENT OWNER regarding the above statement must be submitted promptly to avoid processing delays. Such submission by the patent owner should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation" and will be placed in the reexamination file.

s/

JEAN C. WITZ
PRIMARY EXAMINER

APPENDIX F

Notice of Intent to Issue Ex Parte Reexamination Certificate

Control No. 90/007,064
Patent Under Reexamination 5004681
Examiner Bennett Celsa
Art Unit 3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ Prosecution on the merits is (or remains) closed in this ex parte reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. *Cf.* 37 CFR 1.313(a). A Certificate will be issued in view of

   (a) ☐ Patent owner's communication(s) filed: _____.

   (b) ☐ Patent owner's late response filed: ____.

   (c) ☐ Patent owner's failure to file an appropriate response to the Office action mailed: _____.

   (d) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).

   (e) ☐ Other: ____.

Status of Ex Parte Reexamination:

(f) Change in the Specification: ☐ Yes ☒ No

(g) Change in the Drawing(s): ☐ Yes ☒ No

(h) Status of the Claim(s):

(1) Patent claim(s) confirmed: 1-5.

(2) Patent claim(s) amended (including dependent on amended claim(s)): _____

(3) Patent claim(s) cancelled: _____

(4) Newly presented claim(s) patentable: _____

(5) Newly presented cancelled claims: _____

2. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."

3. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).

4. ☒ Note attached LIST OF REFERENCES CITED (PTO/SB/08).

5. ☐ The drawing correction request filed on ____ is: ☐ approved ☐ disapproved.

6. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
☐ been received.
☐ not been received.
☐ been filed in Application No.
☐ been filed in reexamination Control No.
☐ been received by the International Bureau in PCT Application No. _____

* Certified copies not received: _____

7. ☐ Note attached Examiner's Amendment.

8. ☒ Note attached Interview Summary (PTO-474).

9. ☐ Other: _____

s/
PADMASHRI PONNALURI
CRU EXAMINER - AU 3991

s/
DEBORAH D. JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT

s/
Bennett Celsa
Primary Examiner
Art Unit: 3991

cc: Requester (if third party requester)

UNITED STATES DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

REEXAMINATION

REASONS FOR PATENTABILITY / CONFIRMATION

Reexamination Control No. 90/007,064
Attachment to Paper No. 20061107.
Art Unit 3991.
See Attached

s/_____
(Examiner's Signature)

PTOL-476 (Rev. 03-98)

s/
PADMASHIRI PONNALURI
CRU EXAMINER - AU 3991

s/
DEBORAH D. JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT

STATEMENT OF REASONS FOR PATENTABILITY AND/OR CONFIRMATION

Status of the Claims

Patent claims 1-5 of U.S. Pat. No. 5,004,681 are confirmed.

Instant claim 1 as herein summarized is representative:

> A cryopreserved therapeutic composition comprising:
>
> a. viable human fetal or neonatal hematopoietic stem cells; collected from umbilical cord or placental blood of a single human, present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and
>
> b. an amount of a cryopreservative sufficient for cryopreservation of said cells.

Claim Interpretation:

The patentee June 28, 2006 response with accompanying Zander Declaration (response page 7) and the November 7, 2006 Interview Summary record (page 5) correctly pointed out that the term "hematopoietic reconstitution" as instantly claimed refers to the repopulation of a patient's hematopoietic reconstitution, including blood and bone marrow, with stem cells derived from a donor, allowing the patient to resume normal living. This definition finds support in the instant patent

specification in which the patentee indicates that "[R]econstitution of the hematopoietic system has been accomplished by bone marrow transplantation" ('645 patent col. 2 lines 65-67 concluding:

> Thus, stem and progenitor cells in donated bone marrow can multiply and replace the bone cells responsible for protective immunity, tissue repair, clotting, and other functions of the blood. In a successful bone marrow transplantation, the blood, bone marrow, spleen, thymus and other organs of immunity are repopulated with cells derived from the donor. `645 patent col.3, lines 9-13.

Accordingly, a "sufficient amount" of cord or fetal derived stem cells is that amount of stem cells which reconstitutes or repopulates the adult patient's hematopoeitic system.

The Resections and Rationale for Withdrawal:

1. Claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(b) as anticipated by Douay et al. Exp. Hematol. Vol. 14(5): 358-65 (June1986) as evidenced by the 5,004,681 patent regarding the definition of "neonatal or fetal" stem cell as being an identifier of source and as evidence of inherency.

2. Claims 1-2 are rejected under 35 U.S.C. 102(e) as anticipated by Naughton et al. US Pat. No. 4,721,096 (issued Jan. 26,1988: effectively filed April 18, 1986) as evidenced by the 5,004,681 patent regarding the definition of "neonatal or fetal" stem cell as being an identifier of source and as evidence of inherency.

3. Claims 1-2 and 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. patent '096 as applied to claims 1-2 above, and further in view of Douay et al. Exp. Hematol. Vol. 14(5): 358-65 (June 1986).

Discussion:

The above-rejections rely on the rationale that human stem cells isolated from bone marrow (as in Douy et al. Exp. Hematol. or Naughton) would be expected to be the same as stem cells isolated from the fetal circulation. This rationale was sufficiently rebutted by the patentee's argument, as supported by the cited prior art references, that stem cells found in fetal cord blood are less immunologically mature than marrow adult stem cells. See June 28, 2006 response at pages 21-22.

4. Claims 1-5 are rejected under 35 U.S.C. 102(b) as anticipated by Koike, Acta Paediatrica Japonica 25: 275-283 (1983) as further evidenced by Knudtzon Blood 43: 357-61(1974), Prindull Acta Paediatr. Scand. 67: 413-16 (1978), Douay et al. Exp. Hematol. Vol. 14(5): 358-65 (June 1986), Kessinger Exp. Hematol. 14:192-96 (1986) or Reiffers Exp. Hematol. 14: 312-15 (1986) as evidence of inherency.

5. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koike reference as applied to claims 1-5 above, and further in view of Zelman U.S. Pat. No. 4,306,556 (12/81).

6. Claims 1-5 are rejected under 35 U.S.C. 102(b) as anticipated by Koike, Acta PaediatricaJaponica 25: 275-283 (1983) as further evidenced by

Knudtzon Blood 43: 357-61(1974), Prindull Acta Paediatr. Scand. 67: 413-16 (1978), Douay et al. Exp. Hematol. Vol. 14(5): 358-65 (June 1986), Kessinger Exp. Hematol. 14:192-96 (1986), Reiffers Exp. Hematol. 14: 312-15 (1986) or Ende VA Medical Monthly, 99: 276-280 (1972) as evidence of inherency and enablement.

7. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Douay et al. Exp. Hematol. Vol. 14(5): 358-65 (June 1986), Koike, Acta Paediatrica Japonica 25: 275-283 (1983), Knudtzon Blood 43: 357-61(1974) and Ende VA Medical Monthly, 99: 276-280 (1972).

Discussion:

Patentee's arguments (June 28, 2006 response pages 5-9) and the Zander Declaration and Douay reference teaching were persuasive to overcome the aspect of the above anticipation rejection (item 4 rejection above) asserting inherent anticipation using Koike's 1 millimeter samples. Additionally, patentee's argument that obtaining 10 milliliters (ml) of processed cord blood from pooling Koike's samples is neither disclosed nor specifically suggested by the Koike reference was found persuasive. Further there is no evidence of record to support a teaching that 10 ml of processed core blood would contain sufficient human pluripotential stem cells to reconstitute an adult's hematopoeitic system as required by the instant claims. Accordingly, the disclosed Koike reference's cryopreserved viable human stem cell containing compositions fail to inherently contain an adult hematopoietic reconstituting amount of stem cells.

With respect to the obviousness of claim 3 (item 5 rejection above) patentee's argument that Koike fails to disclose or suggest cryopreserving stem cells in whole blood as required by the plain meaning of these claims was found persuasive.

To the extent that the above anticipation and obviousness rejections (in items 4-7 above) rely on the Koike reference "suggestion" that pluripotent and nearby progenitor cells present in cord blood "may be useful as one of the sources of hemopoietic progenitor cells for marrow transplantation" (Koike at page 281, bottom paragraph to right column), such a suggestion would not have been enabled at the time of the instant invention for the reasons argued and discussed in the submitted declarations of record and the Zander, Bernstein, Bard and Bronxmeyer declarations. This is true since the Koike reference results points toward the equivalency of cord-blood and bone marrow as possessing comparable amounts of progenitor cells per unit volume, which would lead to the teaching that large amounts of cord blood (e.g. 700-900 ml) would indeed be necessary in order to obtain sufficient stem cell amounts to reconstitute a human adult hematopoietic system. In this regard, the presence of at most 100 ml of fetal blood from a single cord, would necessitate the pooling of at least seven different cord samples from different mothers, which in light of HLA matching would be prohibitive.

Additionally, the state of the prior art at the time of the instant invention was made concerning fetal stem cell reconstitution was insufficient to enable the Koike suggestion of employing cryopreserved fetal cord blood. At the time of the

instant invention the use of cord blood for hematopoeitic reconstitution had never been accomplished. Additionally, in vitro expansion of cord-blood stem cells prior to patient implantation had not been successfully employed, and indeed is not in use as of today as indicated by the Dr. Zander declaration. Accordingly, determination of a pharmaceutically efficacious and safe dosage that results in human adult hematopoietic reconstitution would necessarily require undue experimentation, thus precluding enablement. In this respect, it was patentee's in vitro progenitor assays taken in conjunction with in vivo mice testing showing hematopoietic reconstitution with a relatively small amount of neonatal blood, that provided the necessary teaching to enable the obtaining of effective hematopoietic reconstituting dosages in children (extrapolatable to adults) by utilizing cord blood volumes (50-100 ml) derived from a single adult. Thus, neither the Koike reference taken alone anticipates, nor a combination of references render obvious, the instantly claimed invention. It is also further noted that patentee's total evidence of secondary considerations (evidence of copying, licensing and commercial success) weighs strongly toward the nonobviousness of the instantly claimed invention.

Any comments considered necessary by PATENT OWNER regarding the above statement must be submitted promptly to avoid processing delays. Such submission by the patent owner should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation" and will be placed in the reexamination file.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah D. Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Please mail any communications to:

Attn: Mail Stop "Ex Parte Reexam"
Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

Please FAX any communications to:
(571) 273-9900
Central Reexamination Unit

Please hand-deliver any communications to:
Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level
401 Dulany Street
Alexandria, VA 22314

Any inquiry concerning this communication or earlier communications from the Reexamination

Legal Advisor or Examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-7705.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

s/
Bennett Celsa
Primary Examiner
Art Unit 3991

Conferees:

s/
PADMASHRI PONNALURI
CRU EXAMINER - AU 3991
s/
DEBORAH JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT

APPENDIX G

Notice of Intent to Issue Ex Parte Reexamination Certificate	Control No. 90/007,091	Patent Under Reexamination 5192553	
	Examiner Padmashri Ponnaluri	Art Unit 3991	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ Prosecution on the merits is (or remains) closed in this ex parte reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. Cf. 37 CFR 1.313(a). A Certificate will be issued in view of

   (a) ☒ Patent owner's communication(s) filed: 07 November 2006.

   (b) ☐ Patent owner's late response filed: _____

   (c) ☐ Patent owner's failure to file an appropriate response to the Office action mailed: _____

   (d) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).

   (e) ☐ Other: _____

Status of Ex Parte Reexamination:

(f) Change in the Specification: ☐ Yes ☒ No

(g) Change in the Drawing(s): ☐ Yes ☒ No

(h) Status of the Claim(s):

(1) Patent claim(s) confirmed: 13-54 and 57-64.

(2) Patent claim(s) amended (including dependent on amended claim(s)):_____

(3) Patent claim(s) cancelled: 1-12, 55 and 56.

(4) Newly presented claim(s) patentable:_____

(5) Newly presented cancelled claims:_____

2. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."

3. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).

4. ☒ Note attached LIST OF REFERENCES CITED (PTO/SB/08).

5. ☐ The drawing correction request filed on _____ is: ☐ approved ☐ disapproved.

6. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).

   a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have

   ☐ been received.
   ☐ not been received.
   ☐ been filed in Application No._____
   ☐ been filed in reexamination Control No._____
   ☐ been received by the International Bureau in PCT Application No._____

   * Certified copies not received:_____

7. ☐ Note attached Examiner's Amendment.

8. ☐ Note attached Interview Summary (PTO-474).

9. ☐ Other:_____

BENNETT M. CELSA EXAMINER – AU 3991	DEBORAH D. JONES SPRE-AU 3991 CENTRAL REEXAMINATION UNIT	Padmashri Ponnaluri Primary Examiner Art Unit: 3991
s/	s/	s/

REEXAMINATION

REASONS FOR PATENTABILITY / CONFIRMATION

Reexamination Control No.
90/007,091

Attachment to
Paper No. *20061211*.

Art Unit *3991*.

s/
(Examiner's Signature)

s/

BENNETT M. CELSA
CRU EXAMINER –
AU 3991

s/

DEBORAH D. JONES
SPRE–AU 3991
CENTRAL REEXAMINATION
UNIT

Re-Examination

This is a re-examination of US Patent 5,192,553, issued on 09 March 1993.

The Petition under 37 CFR 1.137(b) filed by Patent owner on 11/7/06 was Granted on 12/1/06.

The summary of Interview with Examiner on 9/21/06, filed by the Patentee on 11/7/06 has been considered.

Patentee filed a response, Dr. Zander declaration, Judith Bard declaration, Broxmeyer declaration, and Didier declaration on 7/25/06, in response to the non-final office action mailed on 5/25/06.

Status of Claims

Claims 1-64 were originally present in the 5,192,553 patent.

Original claims 1-12 and 55-56 are canceled by the amendment filed on 4/4/05.

Claims 13-54 and 57-64 are the original claims pending in this reexamination proceedings.

STATEMENT OF REASONS FOR PATENTABILITY AND/OR CONFIRMATION

The following is an examiner's statement of reasons for patentability and/or confirmation of the claims found patentable in this reexamination proceeding:

In view of Patentee's response and Declarations by Dr. Zander, Judith Bard, Broxmeyer, and Didier the prior art rejections of record have been withdrawn and the reasons in detail have been discussed below.

1. The rejection of claims 13-14, 19, 21-23, 25, 28, 47, 53 and 57-58 under 35 U.S.C. 102(b) as being anticipated by Koike as further evidenced by Douay, Ende et al, Knudtzon, Kessinger et al and Reiffers et al as evidence of inherency and enablement, set forth in the previous office action mailed on 5/25/06, has been withdrawn for the reasons discussed in the response and declarations filed on 7/25/06 (see pages 9-22) and for the reasons discussed below.

Koike teaches 'Studies on autologous bone marrow transplantation for child-hood cancer, the viabilities of several kinds of hemopoietic progenitor cells after cryopreservation was assayed using bone marrow and cord blood samples' and 'supporting the usefulness of autologous marrow transplantation for the rescue of the ruined hemopoiesis after intensive cancer therapy.' Thus Koike suggests the use of the hematopoietic stem cells in the treatment of a human patient in need of hematopoietic reconstitution.

However, Koike does not provide an enabling teachings for 'introducing the blood components into a suitable human host to achieve hematopoietic reconstitution' as required by the current claims. Neither Koike reference, nor the additional prior art references cited (as evidence of inherency and enablement) teach *in-vitro* and *in-vivo* tests in Mice model to determine the amount of cord-blood cells

sufficient for hematopoietic reconstitution in humans without undue experimentation.

2. The rejection of claims 57-58 were rejected under 35 U.S.C. 102(b) as anticipated by Douay, as evidenced by U.S. Patent No. 5,192,553, set forth in the previous office action mailed on 5/25/06, has been withdrawn for the reasons discussed in the response and declarations filed on 7/25/06 (see pages 22-25) and for the reasons discussed below.

Douay teaches cryopreserved human bone marrow hematopoietic stem cells, and methods of hematopoietic reconstitution in human adult by introducing the cryopreserved human bone marrow hematopoietic stem cells into a human patient in need of hematopoietic reconstitution.

Patentee argued that stem cells derived from a neonatal source are not identical to those derived from bone marrow. Stem cells derived from bone marrow are immunologically mature compared to the stem cells derived from cord blood. The stem cells from cord blood are capable of safely and effectively carrying out hematopoietic reconstitution without severe GVHD (see Zander declaration). Further, Douay does not teach that it was known in the art what amount of fetal stem cells was sufficient to effect hematopoietic reconstitution or methods to determine the sufficient amount of stem cells for hematopoietic reconstitution. Patentee disclosed the *in vivo* experimentation in animal model to determine the amount of fetal stem cells sufficient to effect hematopoietic reconstitution in human in need thereof. The Patentee's *in-vitro* and *in-vivo* studies established that cord blood contained a substantially

higher progenitor cells than a comparable amount of bone marrow cells. Thus the stem cells derived from cord blood are different from the stem cells derived from bone marrow.

3(a). The rejection of claims 13-14, 19-23, 25, 28-30, 47-48, 53-54, and 60-61 were rejected under 35 U.S.C. § 103(a) as obvious over Koike, Rubenstein (U.S. Patent No. 5,789,147), Ende and/or Reiffers, set forth in the previous office action mailed on 5/25/06, has been withdrawn for the reasons discussed in the response and declarations filed on 7/25/06 (see pages 25-30) and for the reasons discussed below.

The reasons for withdrawing Koike as anticipatory reference were discussed supra. Further, Koike suggests that cord blood contains many pluripotent and nearby progenitor cells comparable to marrow cells, indicate that fetal hematopoietic cells or organs may be useful as one of the sources of hematopoietic cells for marrow transplantation. Koike suggestion implies that cord blood and bone-marrow are comparable in volume amounts of pluripotent and nearby progenitor cells, and several hundred mL of the cord blood is required for successful reconstitution in humans. The Patentee's *in-vitro* and *in-vivo* studies established that cord blood contained a substantially higher progenitor cells than a comparable amount of bone marrow cells. The amount of stem cells (derived from cord blood) capable of contributing to hematopoietic reconstitution is much higher than the bone marrow stem cells. The Patentee's *in vivo* animal model system is used to determine that progenitor and stem cells in cord blood were in fact

effective in achieving hematopoietic reconstitution and to determine the volumes and cell doses comparable with those achievable in humans.

Rubenstein is filed after the effective filing date of the present patent (the '553 patent), thus Rubenstein is not a prior art.

Ende reference failed to achieve long term engraftment and survival of the transplant patient. The transplant patient in the Ende reference did not obtain hematopoietic reconstitution. Ende does not provide a reasonable expectation of success in cord-blood hematopoietic reconstitution, since Ende did not achieve hematopoietic reconstitution in the patient.

Reiffers suggest an amount of cryopreserved autologus peripheral blood mononuclear cells, which is far excess of what could be obtained from a single cord blood sample. Thus Reiffers does not provide any reasonable expectation of success for human hematopoietic reconstitution using cord blood.

Thus for the reasons discussed, the prior art references of record, Koike, Ende and Reiffers individually or in combination do not teach presently claimed method of hematopoietic reconstitution in a human using hematopoietic stem cells derived from a neonatal source.

Further in view of evidence of secondary considerations (efforts by others to copy the invention; Licensing or other acquiescence by the market treating the patentee as the inventor; and commercial success of the invention) provided by the

Patentee (see response pages 38-39), the obviousness rejections of record have been withdrawn.

3(b) The additional claims in the patent, which were rejected under 35 USC 103 over Koike, Ende and Reiffers, additionally in view of one or more of Zelman, Deeg, Beaujean, Shiraki, Maggio-Price, Pillow, Santos, Naughton, Thomas, Wagemaker, Salser, and Stella, have been withdrawn for the reasons discussed supra.

The primary references in these rejections, Koike, Ende and Reiffers do not teach or suggest that cryopreserved fetal stem cells would obtain hematopoietic reconstitution of a human patient in need of hematopoietic reconstitution. For the reasons discussed supra, Koike, Ende and Reiffers individually or in combination with other secondary references do not teach presently claimed method of hematopoietic reconstitution in a human using hematopoietic stem cells derived from a neonatal source.

4(a) The rejection of claims 13-14, 19-23, 25, 28-30, 47-48, 53-54, and 60-61 were rejected under 35 U.S.C. § 103(a) as obvious over Douay, Koike, Ende, and Knudtzon, set forth in the previous office action mailed on 5/25/06, has been withdrawn for the reasons discussed in the response and declarations filed on 7/25/06 (see pages 33-37) and for the reasons discussed below.

Douay teaches cryopreserved human bone marrow hematopoietic stem cells, and methods of hematopoietic reconstitution in human adult by introducing the cryopreserved human bone marrow

hematopoietic stem cells into a human patient in need of hematopoietic reconstitution. Douay does not teach stem cells derived from neonatal source and methods of hematopoietic reconstitution using fetal stem cells. Koike, Ende and Knudtzon fail to provide motivation and provide any reasonable expectation of success for human hematopoietic reconstitution using cord blood.

Thus for the reasons discussed, the prior art references of record Douay, Koike, Ende and Knudtzon individually or in combination do not teach presently claimed method of hematopoietic reconstitution in a human using hematopoietic stem cells derived from a neonatal source.

Further in view of evidence of secondary considerations (efforts by others to copy the invention; Licensing or other acquiescence by the market treating the patentee as the inventor; and commercial success of the invention) provided by the Patentee (see response pages 38-39), the obviousness rejections of record have been withdrawn.

4(b). The additional claims in the patent, which were rejected under 35 USC 103 over Douay, Koike, Ende, Knudtzon, additionally in view of one or more of Zelman, Deeg, Beaujean, Shiraki, Maggio-Price, Pillow, Santos, Naughton, Thomas, Wagemaker, Salser, and Stella, have been withdrawn for the reasons discussed supra.

The primary references in these rejections Douay, Koike, Ende, Knudtzon, do not teach or suggest that cryopreserved fetal stem cells would obtain hematopoietic reconstitution of a human

patient in need of hematopoietic reconstitution. For the reasons discussed supra, Douay, Koike, Ende, Knudtzon individually or in combination with other secondary references do not teach presently claimed method of hematopoietic reconstitution in a human using hematopoietic stem cells derived from a neonatal source.

5. The statutory double patenting rejection of claims 13-34 over claims 19-39 of U.S. Patent No. 6,569,427 (the '427 patent), set forth in the previous office action mailed on 5/25/06, has been withdrawn for the reasons discussed below and the response filed on 7/25/06 (see pages 39-40).

Patentee argues that the independent claim 13 of the current patent comprises the step "isolating" human neonatal or fetal blood components comprising hematopoietic stem cells derived from the umbilical cord or placental blood of human. The current claim requires that the blood components (hematopoietic stem cells) isolated from the whole blood prior to cryopreservation, prior to thawing and introducing into a suitable host for hematopoietic reconstitution. The reference ('427 patent) claim 19 would not require the step of isolating the blood components prior to cryopreservation prior to thawing or introducing into a suitable host.

Thus the current claims are not identical to the reference claims.

Any comments considered necessary by PATENT OWNER regarding the above statement must be submitted promptly to avoid processing

delays. Such submission by the patent owner should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation" and will be placed in the reexamination file.

Conclusion

6. Original Claims 13-54 and 57-64 are confirmed.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809.

The examiner can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)

All correspondence relating to this Ex parte Reexamination proceeding should be directed to

By Mail to:

Attn: Mail Stop "Ex Parte Reexam"
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Commissioner for Patents
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Conferee:

s/
Padmashri Ponnaluri
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12 December 2006

s/
BENNETT M. CELSA

CRU EXAMINER – AU 3991

s/
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